A Johns Hopkins Press Health Book

Hepatitis C

With the latest information on new treatments

A Complete Guide for Patients and Families

PAUL J. THULUVATH, MD, FRCP

VISIT…



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Paul J. Thuluvath, MD, FRCP

Johns Hopkins University Press
Baltimore

Note to the reader. This book is not meant to substitute for medical care of people with hepatitis C, and treatment should not be based solely on its contents. Instead, treatment must be developed in a dialogue between the individual and his or her physician. Our book has been written to help with that dialogue.

Drug dosage: The author and publisher have made reasonable efforts to determine that the selection of drugs discussed in this text conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the U.S. Food and Drug Administration for use in the diseases for which they are recommended. In view of ongoing research, changes in governmental regulation, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert of each drug for any change in indications and dosage and for warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently used drug.

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To my best friend and wife, Reeja

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I will be forever grateful to my mentor, the late Professor David Triger, for inspiring me to pursue my passion in liver disease and "non-A, non-B" hepatitis during my early training at Sheffield University. Dr. Triger, along with my teachers, colleagues, fellows, and residents at Cambridge University, the University of London, and Johns Hopkins University, have made my career in hepatology very fulfilling. I thank them for this.

Lastly, without my patients and their families I would not have been able to truly grasp the implications of liver disease for everyday life. Their stories have taught me more than I could glean from any books on this topic. Their experiences and their journey with hepatitis C made me recognize how important it is for a patient to have a full understanding of the ramifications of hepatitis C and the curative treatment options available.

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Hepatitis C

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Introduction

Hepatitis C affects between 3 and 4 million people in the United States. Many people who have hepatitis C have not been diagnosed and do not know they have it. Hence, hepatitis C is called the silent epidemic.

During the past 25 years, much progress has been made in the diagnosis and treatment of hepatitis C, starting with the identification of the virus. Despite these advances, successful treatment of hepatitis C remains a major challenge, for many reasons. First, most people who have hepatitis C are not diagnosed, and the medical profession and the public remain uneducated or only partially educated about the disease. Often, the public can get accurate information about the disease only from medical specialists who have an interest in hepatitis C. Moreover, many people do not fully understand and interpret the tests commonly used by physicians. The Internet—a double-edged sword—can provide information to individuals quickly and inexpensively but can also distribute unreliable and inaccurate information through websites that are purely anecdotal.

When a hepatitis C infection remains unnoticed, it progresses to cirrhosis in about one-third of infected people. At that stage, liver transplantation is sometimes the only option. Yet, because of organ shortages, timely transplantation has, for most people, become increasingly difficult. The increasing number of people with liver cancer in the United States and in many other countries suggests that hepatitis C is perhaps one of the leading causes of liver cancer in the world. In addition, an increasing number of children and people with HIV infection are also infected with hepatitis C. It has been suggested that in HIV-positive

individuals, hepatitis C may emerge as a major killer, negating some of the advances that have been achieved in the treatment of HIV.

During the past three years, the treatment for hepatitis C has changed rapidly. Until recently, side effects of interferon, an antiviral medication, were a major problem for people who sought and received treatment for hepatitis C. But now, the introduction of many direct-acting oral medications for hepatitis C is rapidly changing the cure rates for hepatitis C infection. As of the end of 2014, interferon-free treatment has become the standard of care in the United States. A combination of two or three direct-acting antiviral medications taken for 8 to 24 weeks will cure more than 95 percent of people who have hepatitis C.

Despite the advances in treatment, some limitations remain. The high cost of treatment remains prohibitive for many less fortunate people in developed countries and for the majority of people who live in developing countries. The treatment regimen needs to be further refined to safely offer the drugs to children and people who have advanced cirrhosis and kidney failure. The search for a hepatitis C vaccine, which has remained elusive because of the complexity of the virus, is another area of ongoing research.

This book accurately documents the current state of knowledge of hepatitis C. It is for everyone who has been affected by the infection and for medical professionals seeking an overview of diagnosis and treatment. The book's final chapter discusses the role of complementary and alternative medicine for people who have liver disease. We believe that this book will remain an important source of information for all people who have hepatitis C and for everyone involved in their care.

Part I

Understanding Hepatitis C, Liver Disease, and Liver Cancer

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1

Understanding Hepatitis C

According to the World Health Organization, about 3 percent of the world's population, roughly 170 million people, may be infected with the hepatitis C virus. In the United States today, hepatitis C affects approximately 3 to 4 million people (1.4 to 1.8 percent of the population), with 38,000 new cases each year. Although new hepatitis C infections affect people of all ages, individuals between the ages of 20 and 39 are at the highest risk of becoming infected.

Fortunately, there have been and continue to be major advancements in the treatment of hepatitis C. Later in this book, we explore current treatment options and resources, as well as the outlook for the future of hepatitis C treatment.

First, building a solid framework of knowledge will help you ask better questions of physicians, seek the support you need, and make informed decisions. In this chapter, we begin to build that framework by explaining basic definitions, distinctions, and statistics, to help you better understand risk factors for hepatitis C, how hepatitis C is transmitted, and how it is diagnosed. We also discuss the basic functions of the liver and how those can be disrupted because of injury or disease.

What Is "Hepatitis"?

Hepatitis means inflammation of the liver. This inflammation can be caused by many factors, including viruses, toxins, medications, and your own immune system damaging itself (in a process called autoimmunity).

Viral infections, including hepatitis A, hepatitis B, hepatitis C, and hepatitis E, are the most common causes of hepatitis. Hepatitis D (also known as delta virus) is an incomplete virus and requires hepatitis B virus for replication, and therefore it is seen only in those with hepatitis B infection. These viruses invade normal liver cells, called hepatocytes, and use those host cells to multiply and produce other viruses like themselves through a process called replication. The viruses depend on the host cells to replicate—they cannot do it on their own.

Although this book focuses on hepatitis C, understanding the distinctions between the most common viral liver infections will be helpful. Unlike other living organisms, viruses have no cells. Instead, a virus consists of a core of nucleic acid, which can be either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), in a protein capsule. A virus is identified as either an RNA or a DNA virus, depending on the nucleic acid of its core.

Hepatitis A, hepatitis C, hepatitis D, and hepatitis E are RNA viruses, and hepatitis B is a DNA virus. There are some major differences between the two types of viruses, including the way they enter the cell and multiply. RNA viruses multiply in the cytoplasm, and DNA viruses multiply inside the cell's nucleus. Also, they use different enzymes for replication: a DNA virus uses DNA polymerase, and an RNA virus uses RNA polymerase. Because RNA viruses are less stable than DNA viruses, changes in RNA viruses' genetic material or genetic codes, called mutations, occur more often. Viruses mutate to survive, and these changes occur spontaneously or when attempts are made to destroy them, such as with medications.

Both RNA and DNA viruses have been present in humans for thousands of years, and they have even been identified in mummies. In fact, we can trace human migration by carefully examining the genetic material of hepatitis B and C viruses.

Hepatitis A, B, C, and E

Hepatitis A is a liver disease that results from infection with the hepatitis A virus. It is usually spread when a person ingests food or water con-

taminated with fecal matter, even in microscopic amounts, from an infected person. The average incubation period is 28 days and may range from 15 to 50 days. Illness from hepatitis A can range in severity from mild, with jaundice and loss of appetite, to severe, which may result in liver failure. Hepatitis A infection is always a short-term (acute), self-limiting infection, and it never leads to a long-term (chronic) infection. Most people survive and develop lifelong immunity, becoming resistant to future infections. There is no specific treatment for hepatitis A infection; however, severe symptoms, such as nausea and vomiting, can be managed. There is a vaccine to prevent hepatitis A infection.

Hepatitis E is similar to hepatitis A and is usually transmitted when a person ingests food or water contaminated with fecal matter, and only rarely by transfusion of blood products contaminated with hepatitis E or vertically from a hepatitis E–infected pregnant woman to her newborn child. Worldwide, hepatitis E is common (about 20 million infections per year), but it is seen predominantly in the countries of South Asia and other low-income countries. In the United States, a few cases of hepatitis E are reported every year. Hepatitis E, like hepatitis A, never leads to chronic infection, and there is no effective vaccine.

Hepatitis B is a liver disease that is usually transmitted from an infected person to an uninfected person by blood, semen, or other body fluid. The hepatitis B virus can be spread through sexual contact with an infected person or by sharing needles, syringes, or other drug-injection equipment. Hepatitis B may also be passed from an infected mother to her baby at birth. Worldwide, hepatitis B is more common than hepatitis C.

Infections with hepatitis B can be either acute or chronic. Acute hepatitis B infection is a short-term illness that occurs within six months after exposure. The average incubation period is 120 days after exposure to the hepatitis B virus, but it can range from 60 to 150 days. Acute infection can, but does not always, lead to chronic infection. Chronic hepatitis B infection is a long-term, serious illness that occurs when the hepatitis B virus remains in a person's body. There is a vaccine to prevent hepatitis B infection, and there are effective treatments to suppress the infection.

Hepatitis C is a common liver disease that is transmitted from an infected person to an uninfected person through blood or blood products. The risk of spreading hepatitis C is high among those who abuse drugs and have multiple sexual partners. The risk of developing hepatitis C infection through blood transfusion is negligible; rarely, women with hepatitis C can transmit the virus to their infants.

Hepatitis C infection can be either acute or chronic. Acute hepatitis C infection is a short-term illness that occurs after exposure to the hepatitis C virus. The average incubation period after exposure is 45 days and can range from 15 to 180 days. About 30 percent of individuals with acute hepatitis C infection will be spontaneously cured without any treatment. For almost 70 percent of those infected with hepatitis C, acute infection leads to chronic infection. Chronic hepatitis C is a serious disease that can result in long-term health problems, such as cirrhosis and liver cancer, and death. In the past, cure rates were low, but in the past decade, treatment has dramatically improved, and most people can expect an effective cure with medications. Although there is no vaccine for hepatitis C, research in this area is ongoing. We discuss treatment in greater detail in chapters 13 to 16 and chapter 18.

The Discovery of Hepatitis C

In the 1970s and 1980s, the medical profession knew of a bloodborne infectious agent (perhaps a virus or viruses) that was commonly transmitted by transfusion of blood products and could cause chronic liver disease. Because this infectious organism was not yet identified and there were no tests to identify it, as there were for hepatitis A and B, the infection was called non-A, non-B hepatitis. This organism was believed to be a major cause of hepatitis contracted through blood transfusion or intravenous drug use. Many individuals who had abnormal liver test results for months or even years were thought to have had non-A, non-B hepatitis.

In 1989, the discovery of the hepatitis C virus marked a major breakthrough in the understanding of transfusion-related hepatitis, resulting

Table 1.1. Hepatitis C Infection in the United States, 2014

Number of new cases	38,000 per year
Number of new cases (acute hepatitis) with symptoms	6,300 per year
Acute liver failure	Rare
Number with chronic infection	2.7 million (could be as high as 5 million)
Hepatitis C–related deaths per year	8,000 to 10,000
Hepatitis C–related chronic liver disease	40% of all chronic liver disease

in the routine screening of blood products for hepatitis C. Until 1989, the incidence of new hepatitis C infections in the United States had been about 230,000 per year. New infections declined dramatically between 1989 and 1997 to the current rate of 38,000 new cases per year (table 1.1). This decrease was mainly due to safer practices regarding the use of blood products and safer needle-using practices among intravenous drug users. New hepatitis C infections occur in individuals of all ages, but the highest rate of infection is among people between the ages of 20 and 39.

Hepatitis C: The Global Story

Hepatitis C is a common worldwide disease. As noted earlier, about 3 percent of the world's population is infected with hepatitis C, and the rate of chronic hepatitis C infection in the United States is approximately 1.4 to 1.8 percent of the population. The disease is more common in parts of Eastern Europe, parts of Central and South America, and Africa (figure 1.1). In northern Europe, the rate of new infections is similar to that in the United States. By far, Egypt has the highest infection rate, with about 17 to 26 percent of the population infected with hepatitis C. This rate can be mostly attributed to a period between 1960 and 1987 when glass syringes were reused as part of Egypt's nationwide vaccination program to prevent schistosomiasis.

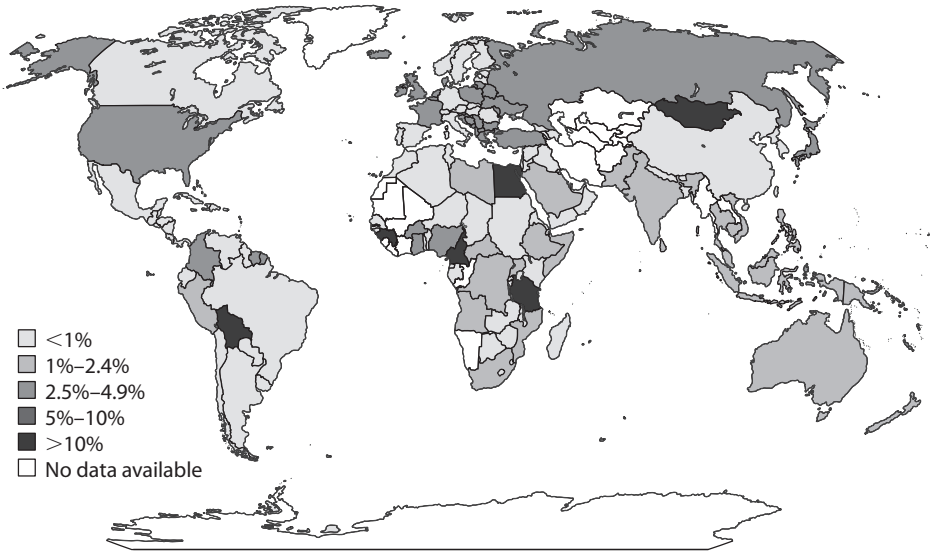


Figure 1.1. Worldwide prevalence of hepatitis C

Hepatitis C Infection Rates Worldwide

In the United States and Australia, the percentage of hepatitis C infection is highest among those born between 1945 and 1965. This fact may indicate that most people who have hepatitis C were infected in the past 40 years. In Japan and Italy, the prevalence is higher in older people and lower in those younger than 40 years old, indicating that many may have also contracted this disease 30 to 50 years ago, with a more recent decline in new infections. In Egypt, evidence indicates that ongoing new infections are occurring at very high rates.

Individuals at the Highest Risk for Hepatitis C Infection

People who live in areas of especially high prevalence, such as Egypt, have a greater risk of being infected with the hepatitis C virus. However, regardless of where they live, the following groups have a higher risk for hepatitis C infection:

- People who are addicted to intravenous drugs and cocaine
- People who are HIV-positive

- People who are in prison
- Males who are homosexual or bisexual
- Hemodialysis patients
- People who have hemophilia
- Individuals with multiple sexual partners
- Sexual partners of those infected with both hepatitis C and HIV
- Recipients of organs from donors with hepatitis C

In October 2012, the Centers for Disease Control and Prevention (CDC) recommended that all individuals born between 1945 and 1965—the baby boomers—be tested once for hepatitis C. So far, testing only those at risk has identified a small number of adults with hepatitis C. Studies show that routine testing of all adults born between 1945 and 1965 could identify as much as 75 percent of the population infected with hepatitis C. Baby boomers have many risk factors for hepatitis C and are five times more likely to have the disease than other adults. Their reluctance to admit those risk factors to their physicians could be one of the reasons for this high rate of undiagnosed infection, although the exact reasons are not well known. The CDC estimates that one-time testing would diagnose an additional 800,000 adults with hepatitis C, and treatment of these adults might prevent as many as 120,000 deaths resulting from chronic hepatitis C in the future. You can find more information about hepatitis C on the CDC's website (www.cdc.gov/hepatitis/c).

Although most people with hepatitis C have one or more of the hepatitis C risk factors mentioned above, about 10 to 40 percent of infected individuals have no risk factors.

How Is Hepatitis C Spread?

The hepatitis C virus is spread through blood or blood products. To cause infection, the hepatitis C virus must pass from the blood of an infected person to the blood of an uninfected person (figure 1.2). The most common direct ways of spreading hepatitis C are

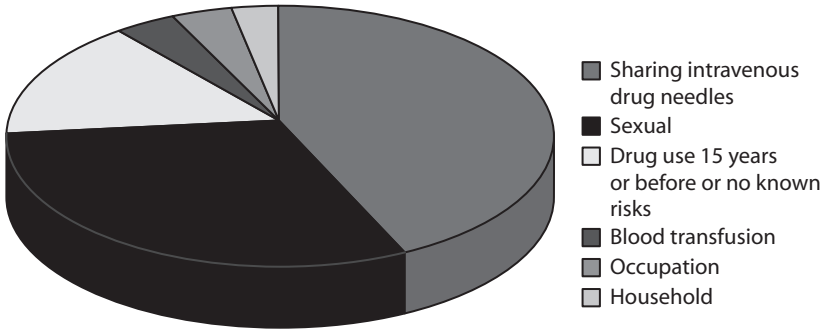


Figure 1.2. Risks for acute hepatitis C in the United States

- Sharing intravenous drug needles with an infected person
- Snorting cocaine
- Having sex with an infected person
- Getting a blood transfusion from an infected person
- Getting a tattoo
- Sharing toothbrushes or razors with an infected person
- Receiving an organ from an infected donor

Intravenous or Intranasal Drug Use

Most hepatitis C infections are spread by sharing intravenous drug needles or by sharing a straw when snorting cocaine. The use of injection drugs accounts for up to 60 percent of all infections. After five years of injection drug use, as many as 90 percent of users are infected with the hepatitis C virus. Sharing a straw when snorting cocaine can also spread hepatitis C, but, to date, there are only limited studies showing a relationship between hepatitis C and snorting cocaine independent of injection drug use.

Sexual Contact

The risk of becoming infected with hepatitis C through sexual contact is very low. Among individuals whose spouses have hepatitis C, less than 5 percent are infected with the disease. The prevalence of hepatitis C infection is 1.3 percent among spouses or partners in stable monogamous relationships and having no other reported risk factors, a rate similar

to that for the general population. The medical profession currently makes no recommendations regarding hepatitis C and sexual practices, especially for those with long-standing monogamous relationships. However, if couples want to further reduce their risk, they should use condoms.

The prevalence of hepatitis C infection is higher among individuals with high-risk sexual practices, including the following groups:

- Males who have sex with males, and females who have sex in exchange for money
- Sexual partners of people who use drugs intravenously
- People with multiple sexual partners
- People who have sex with both men and women
- People who are HIV-positive

In these groups, the factors that increase the risk of hepatitis C infection include having a history of other sexually transmitted diseases, multiple sexual partners, failing to use a condom, and participating in traumatic sexual activities. The risk of sexual transmission is also higher if the infected person's immune system is weakened, which allows the hepatitis C virus to multiply quickly in the blood.

Blood Transfusions

In the United States today, the risk of developing hepatitis C from a blood transfusion is negligible. The risk of getting infected with hepatitis C from blood transfusions has decreased dramatically over the past 20 years because all potential blood donors are tested for hepatitis C antibodies.

Before 1990, potential blood donors could not donate if they had elevated liver enzymes or a history of jaundice. This guideline alone reduced the infection rate from 5 to 13 per 100 blood transfusions to less than 1 per 100 transfusions. People with hemophilia who received untreated blood factor concentrates before 1990 have hepatitis C infection rates of more than 90 percent.

Since 1990, all donors have been tested for hepatitis C antibodies. More recently, pooled blood from multiple donors is tested using a more sensitive and accurate blood test, called hepatitis C RNA by polymerase

chain reaction (PCR). If the test is positive with pooled blood, all donors in the pool are tested for hepatitis C RNA by PCR. Testing blood in this manner removes from the blood donor pool the risk of missing any potential donors who do not have hepatitis C antibodies but have circulating virus. In addition, to further reduce the risk of spreading hepatitis C through blood transfusion, more accurate and sensitive testing is now done to identify potential blood donors who may have hepatitis C in their blood but do not have any detectable hepatitis C antibodies. Because of improved blood processing procedures, the risk of contracting hepatitis C through blood transfusion is minuscule in the United States.

In areas of the world where blood screening is not done, these exposures remain an important risk for infection. The World Health Organization (Global Database of Blood Safety) estimates that 43 percent of blood donors in many developing countries are not tested for hepatitis C. Even in countries, such as India, where the law mandates compulsory screening of all donors for hepatitis C, many laboratories do not follow these laws, for financial reasons. In many developing countries, paid donors are commonly used, and, in the absence of mandatory testing, using these donors further increases the risk.

Tattoos

Getting a tattoo carries a risk of infection if the tattoo artist fails to use strict safety procedures, because the process involves piercing the skin with a needle and injecting a tiny amount of ink. If the needle is clean and new (not used before), there is no risk.

Other Practices

Body piercing, commercial barbering, circumcision, and scarification have the potential to spread hepatitis C. However, there are no current studies that demonstrate a definite causal link between these practices and hepatitis C infection.

Medical or Dental Procedures

Hemodialysis carries a high risk of hepatitis C infection, and the risk increases the longer the person remains on hemodialysis. The mode of

transmission is not well understood, but sharing of the dialysis machine, blood transfusions, and disruption of standard infection-control practices may be responsible for the higher prevalence of hepatitis C in dialysis patients.

Worldwide, approximately 2 to 3 percent of individuals receiving hemodialysis get newly infected every year from hemodialysis. However, the hepatitis C infection rates from hemodialysis vary widely across different regions. The United Kingdom and South Africa have reported the lowest rates (1 to 5 percent), North America, Scandinavia, Western Europe, and Asia have reported intermediate rates (10 to 50 percent), and Eastern Europe has reported the highest rates (20 to 91 percent). As precautions to prevent hepatitis C transmission improve, infection rates will continue to decrease.

The risk of patients becoming infected with hepatitis C from infected healthcare workers during surgical procedures appears to be very low. There have been only very few case reports of such transmission worldwide, mostly involving cardio-thoracic surgeons infected with hepatitis C.

Risk within the Family

The risk of spreading hepatitis C among household members who are not sexual partners is extremely low—studies from North America and Western Europe show 0.7 percent (7 in 1,000) of household contacts with hepatitis C antibodies. The mode of nonsexual transmission is not clear but could include sharing toothbrushes, razors, and nail-grooming equipment.

The risk of women with hepatitis C infecting their infants is low—fewer than 6 in 100 infants, or 6 percent. For women who are infected with both hepatitis C and HIV, however, the risk is higher, about 17 percent, because of their high hepatitis C viral blood counts. Having a cesarean section rather than a vaginal delivery has no effect on the transmission rate.

Transmission of hepatitis C from mother to infant by breast milk has not been proven. If a risk exists, it is extremely low.

Occupational Exposures

Healthcare workers who potentially are exposed to blood are at increased risk for hepatitis C infection, and the rate of hepatitis infection in this group appears to be higher than in the general population. The risk of acquiring hepatitis C infection after a single needle-stick injury is low, estimated at 1.8 percent by some studies, and ranging between 0 and 7 percent. The risk of spreading the disease is highest with the use of hollow-bore needles. Transmission of hepatitis C by blood splashes to the eye has also been reported. At work, healthcare workers can protect themselves from infection by wearing two pairs of gloves and protective goggles and by minimizing their exposure to sharp instruments and needles.

The relative risk of transmission of hepatitis C, hepatitis B, and HIV is shown in figure 1.3.

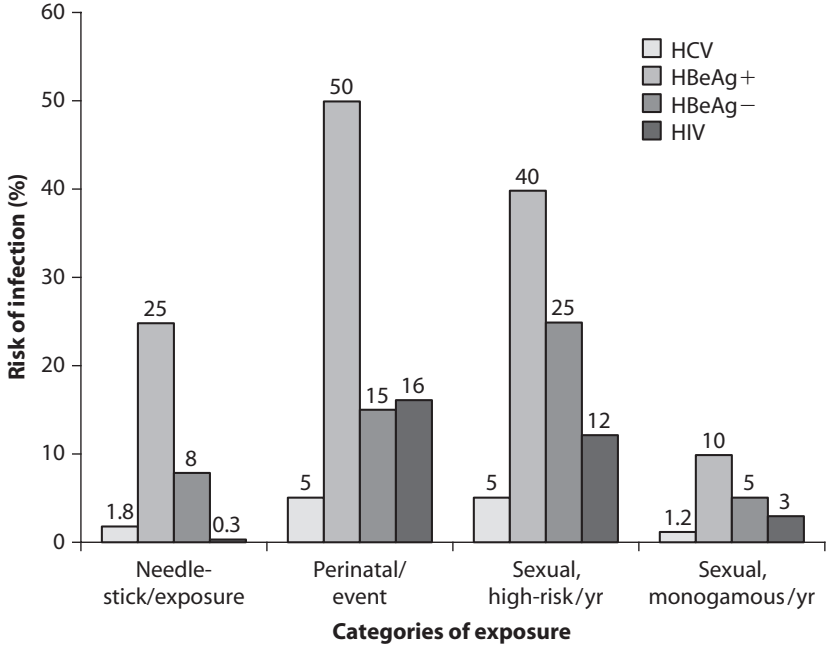


Figure 1.3. Transmission risks for hepatitis C (HCV); hepatitis B (shown as $HBeAg^+$, meaning the virus is replicating and blood tests show HBeAg, and $HBeAg^-$, meaning the virus is replicating but has mutated and does not express HBeAg, and therefore blood tests will not show HBeAg); and HIV. The risk is highest for hepatitis B.

Activities That Present No Transmission Risk

If you have hepatitis C, you may feel frightened about the possibility of spreading the virus to a family member or friend. There are specific risks for spreading the virus, as we have noted. But hepatitis C is transmitted between people only through blood or blood products—unlike hepatitis A, which is spread by ingesting contaminated food or water. The key to living the fullest possible life is understanding the difference between risky and safe behaviors. Most daily activities, including the following, are safe and carry no risk of infection:

- Sharing food or drinks
- Living in the same household
- Kissing, hugging, shaking hands
- Close, nonsexual body contact

Understanding How the Liver Works

The Workhorse Organ

The liver, the body's largest solid organ, weighs about three pounds. It is located in the upper part of the abdomen on the right side and has two large sections, the right and left lobes (figure 1.4). The gallbladder sits under the liver, along with parts of the pancreas and intestines (figure 1.5). The liver and these other organs work together to digest, absorb, and process food.

To say the liver is a workhorse is an understatement. The major functions of the liver (see table 1.2) include the following:

- To make proteins, including albumin and blood clotting factors
- To synthesize, store, and process fats, including fatty acids (used for energy) and cholesterol
- To metabolize and store carbohydrates (used as the source for the sugar in blood)
- To form and secrete bile, which contains bile acids, to aid in the intestinal absorption of fats and the fat-soluble vitamins A, D, E, and K

- To eliminate, by metabolizing or secreting, the potentially harmful biochemical substances produced by the body, such as bilirubin, from the breakdown of old red blood cells, and ammonia, from the breakdown of proteins
- To detoxify, by metabolizing and/or secreting, drugs, alcohol, and environmental toxins

Liver Injury or Damage

Injury to the liver, through whatever process, results in damage to the liver cells (hepatocytes), small bile ducts, or, in some cases, both. When liver cells are damaged or injured (commonly by medications), liver enzymes are released into the bloodstream. The injury to the liver could be a direct effect or could be caused by the inflammatory process of the person's immune system. The healing process of this injury results in scar formation (fibrosis).

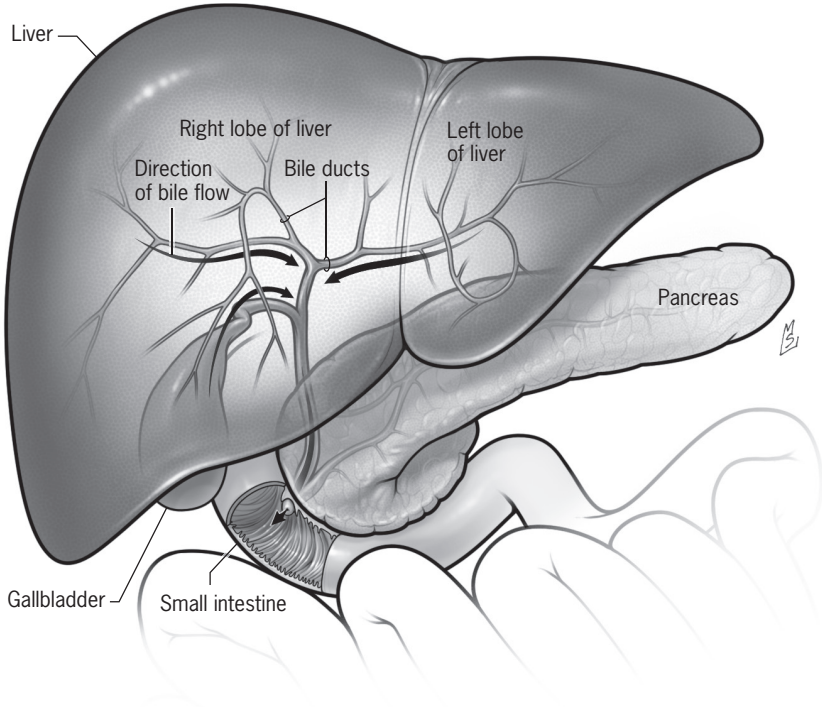


Figure 1.4. The anatomy of the liver, gallbladder, and pancreas

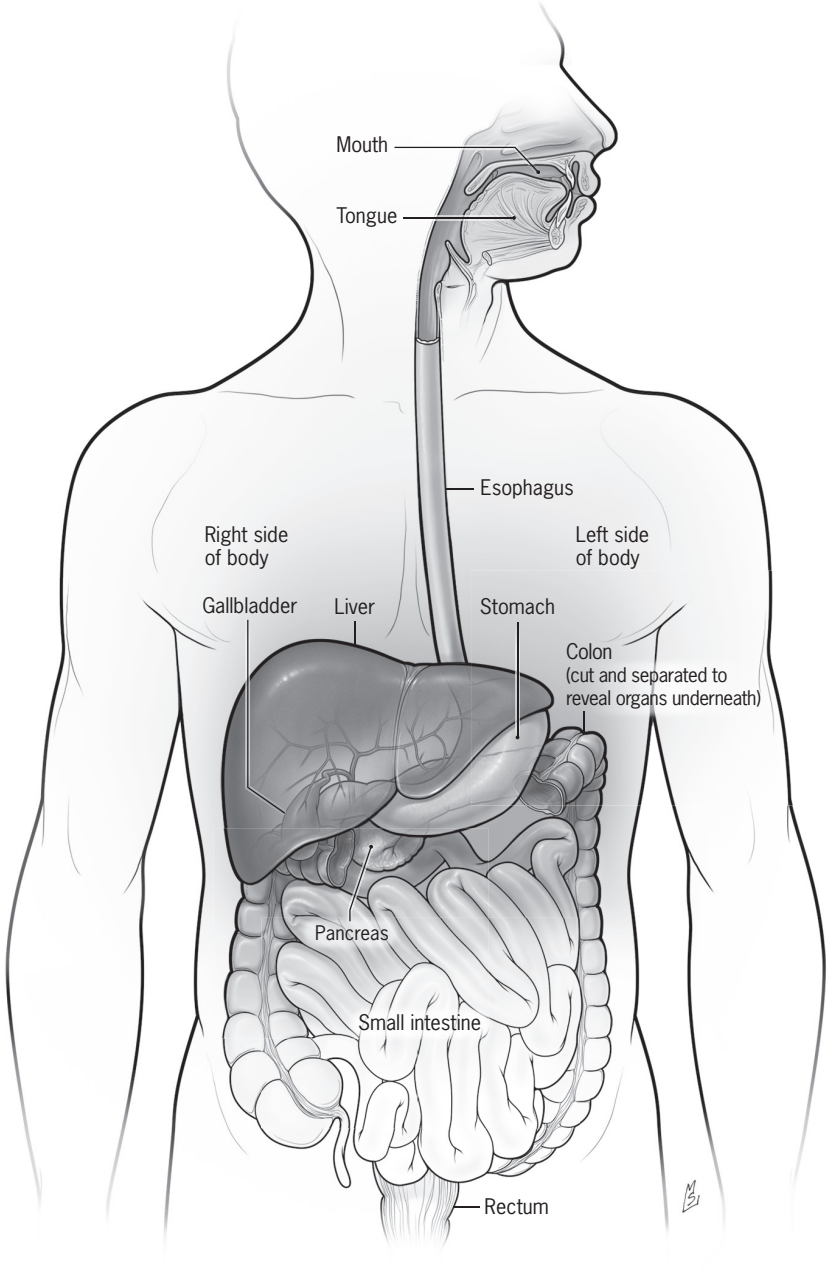


Figure 1.5. The anatomy of the digestive system

Table 1.2. Important Functions of the Liver

Plays a major role in the metabolism of carbohydrates, proteins (amino acids), and lipids (cholesterol and triglycerides).
Makes proteins, including albumin (to help maintain the volume of blood), fibrinogen (necessary for blood clotting), transferrin (iron-transporting protein), prothrombin (clotting factor), and others.
Metabolizes many drugs.
Removes many toxins, including ammonia, from the breakdown of proteins, and bilirubin, from the breakdown of old red blood cells.
Removes tumor cells, bacteria, yeasts, viruses, and parasites, using its specialized cells (such as Kupffer cells).
Stores many vitamins and minerals.

Fortunately, the liver can withstand a lot of injury. Even with mild to moderate injuries, a person will most likely not have any symptoms. In acute situations, the appearance of symptoms, such as jaundice, indicates significant liver damage. When the cause of damage is removed in acute situations, the liver can repair itself (regenerate liver cells) and return to its normal state. However, in chronic situations, this repair is not always possible. When there is more scar formation, the liver slowly becomes shrunken, lumpy (nodular), and hard—a condition known as cirrhosis of the liver.

Until recently, physicians believed that cirrhosis was irreversible. New evidence indicates that there is a small possibility that early cirrhosis can be reversed if the cause of damage is removed (for example, hepatitis C is cured). Fibrosis is now believed to be a dynamic process, and, in the future, medications could be developed to reverse cirrhosis. This is an exciting field of research for scientists.

As with acute liver injury, chronic injury does not cause any symptoms until there is significant damage to the liver. Many people do not develop symptoms until the late stages of cirrhosis. Therefore, it is important to manage liver disease irrespective of symptoms. In addition, about 1 in 10 people with cirrhosis may have normal results on liver enzyme tests. Many people do not want to receive treatment for chronic

hepatitis C because they feel well, and they often ask physicians, "Why fix it if it's not broken?" This approach is dangerous because by the time symptoms appear, it may be too late to fix the problem.

In chapter 2 we describe how hepatitis C is diagnosed, including an overview of testing for the hepatitis C virus.

2

Diagnosing Hepatitis C

Who Should Be Tested for Hepatitis C?

If you have any of the hepatitis C risk factors listed in chapter 1, you should get a blood test for hepatitis C, even if you feel fine and have no symptoms. Many people with an acute hepatitis C infection have no symptoms, and their liver enzymes may be within the normal range. A normal liver enzyme test result does not rule out hepatitis C infection or liver disease. In fact, a significant number (10 to 30 percent) of people who have normal liver enzyme levels may have advanced liver disease due to hepatitis C or another cause.

Because liver enzyme levels also may fluctuate over time, a single normal measurement may not mean that a person's liver enzymes are always normal. However, if liver enzymes and other liver tests are consistently normal, and there are no other signs or symptoms, the probability of having serious injury to the liver is low.

Anyone with abnormal liver enzymes—even if the elevation of enzymes is very mild—should request a hepatitis C test. Testing is especially important for those who currently have or have had sexual partners who ever abused drugs and for those who currently have or have had sexual partners with HIV or hepatitis C infection. Healthcare providers with a needle-stick history also may choose to be tested. And, although the risk of transmitting infection during birth and through breastfeeding is small, mothers infected with hepatitis C should request testing for their children.

You should request a hepatitis C test if any one of the following conditions, practices, or circumstances applies to you:

- Have liver disease or any elevation of liver enzymes
- Have a history of jaundice
- Have used or currently use intravenous (IV) drugs or cocaine
- Are a healthcare worker with a history of needle-stick injuries
- Had a blood transfusion before 1990
- Have a sexual partner(s) with hepatitis C or HIV infection
- Have a sexual partner(s) who abused drugs at any time
- Have a history of sexually transmitted diseases
- Are receiving hemodialysis treatment
- Have hemophilia
- Are a child of a mother who is infected with hepatitis C

In addition, in October 2012, the Centers for Disease Control and Prevention (CDC) recommended that all people born between 1945 and 1965 consider being tested for hepatitis C even if they have no risk factors.

Common Tests for Hepatitis C Infection

Several types of tests are used to diagnose liver disease (table 2.1).

Table 2.1. What Are the Tests for Liver Disease?

Test	*Purpose*
Liver enzyme levels	If enzymes are elevated, indicates injury to liver cells or bile duct
Hepatitis C antibody test	Indicates present or previous infection
Qualitative hepatitis C RNA by PCR	Confirms ongoing infection
Quantitative tests (PCR)	Measures virus quantity in the blood (counts)
Hepatitis C genotype and subtype	Determines type of hepatitis C virus (1 to 6)
Liver biopsy	Assesses damage to the liver (i.e., severity of inflammation and scarring)

Hepatitis C Antibody Test

When a person is infected with hepatitis C, the immune system produces antibodies against the virus. An antibody is a member of the immunoglobulin class of proteins that are produced and secreted by the B cells of the immune system in response to foreign substances called antigens. Antibodies are found in the tissue fluids and mucous membranes and are essential for protection against and recovery from infection.

The diagnosis of hepatitis C is based on blood tests that look either for antibodies to the hepatitis C virus or for the virus itself. The hepatitis C screening tests most commonly used today are third-generation enzyme immunoassay (ELISA) tests, which diagnose hepatitis C accurately in 95 percent of individuals. Although this rarely occurs, these tests may produce negative results for individuals with hepatitis C whose immune systems are suppressed by an infection or by some medicines, as can happen in people who are HIV-positive or who have received a transplant. The antibody test also may be negative in those with an acute hepatitis C infection, because it may take a few weeks or even months for hepatitis C antibodies to appear in the blood.

The presence of hepatitis C antibodies in the blood does not mean a person has an active hepatitis C infection. The antibody test cannot differentiate between an active hepatitis C infection and a previous hepatitis C infection. This means that anyone who has had a hepatitis C infection and has been cured will always have hepatitis C antibodies in their blood. The antibodies also may appear for a short time in children born to mothers who test positive for hepatitis C.

Individuals without a current or past hepatitis C infection rarely have hepatitis C antibodies in their blood. However, individuals with immune-mediated diseases, such as rheumatoid arthritis, lupus, and autoimmune liver diseases, could have a false-positive result in the hepatitis C antibody test. In general, the test is extremely accurate, and 95 percent of those who have detectable antibodies have ongoing hepatitis C infection.

Hepatitis C Virus Ribonucleic Acid (RNA) by PCR Test

Even if a test reveals antibodies in the blood, another test is necessary to confirm a hepatitis C diagnosis. The polymerase chain reaction (PCR) test is used to detect the presence or quantity of hepatitis C virus ribonucleic acid (HCV RNA) in the blood. The qualitative PCR test detects the presence of tiny traces of hepatitis C virus in blood or other body fluids and detects the genetic material—RNA—of the hepatitis C virus. Determination of HCV RNA by PCR is the most sensitive test currently available.

The quantitative PCR test, which detects the amount of hepatitis C RNA in the blood, is commonly used to assess the treatment response, not to confirm diagnosis. The quantitative PCR result is described in international units (IU) per milliliter (ml) of blood. The use of international units is standardized and can be used to compare values even if the tests are done in different laboratories.

The detection limits of the quantitative PCR test vary, depending on the type of analysis or the laboratory. Some tests can detect as little as 5 IU/ml. The upper detection limit also varies. The test result values do not indicate the severity of liver disease or the prognosis. Although having higher values may frighten those with hepatitis C infection, there is no convincing evidence that the quantity of HCV RNA has any impact on either the progression or the severity of the disease. The only exception is for patients with extremely high HCV RNA levels (usually more than 20 million IU/ml) after organ transplantation, who may develop rapidly progressive liver disease. Higher HCV RNA baseline values also may indicate lower response rates to hepatitis C treatments in certain hepatitis C virus genotypes.

Although many people with hepatitis C infection wish to monitor their HCV RNA values periodically, this practice is not recommended, because the values do not indicate the severity of liver disease or prognosis. Table 2.2 summarizes what the results of antibody and HCV RNA testing mean.

The normal range for liver enzymes varies, depending on the laboratory where the test is performed. Most laboratories use 30 IU/ml as the

Table 2.2. What Do the Test Results Mean?

Test Results	*Meaning*
Hepatitis C antibody = positive	Person is either infected or had previous infection. Rarely, it is false-positive (meaning that the test result is positive in the absence of hepatitis C exposure).
Hepatitis C antibody = positive *and* hepatitis C RNA = positive	Person has active hepatitis infection.
Hepatitis C antibody = positive *and* hepatitis C RNA = negative	Person has no active infection and has cleared the virus (with treatment or spontaneously) or has a false-positive result.

normal upper limit for alanine aminotransferase (one of the liver enzymes) levels. Recently, it has been suggested that the upper normal limit for women should be less than 19 IU/ml.

Genotype Testing

Hepatitis C is a single-stranded RNA virus that belongs to the Flaviviridae family. Its molecular structure, or genome, consists of 9,400 building blocks called nucleotides. Although it is easier to think about the hepatitis C virus as if it were one organism, it is actually a range of viruses different enough from one another genetically to be classified into types called genotypes and, even further, into subtypes. These multiple hepatitis C types and subtypes are determined by differences in as much as 30 percent of the nucleotide sequences over the entire length of the viral genome.

Two classification systems have been developed for hepatitis C genotypes and subtypes. The more popular Simmonds system classifies genotypes and their subtypes as genotypes 1 through 9 and subtypes 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 4c, 5a, 6a, 7a, 7b, 8a, 8b, and 9a. The Okamoto system classifies the virus as types I, II, III, IV, V, and VI, which correspond to types 1a, 1b, 2a, 2b, 3a, and 4 of the Simmonds system.

Identifying the hepatitis C genotype is critical before starting any kind of treatment. The duration of treatment and, to some extent, the dosage

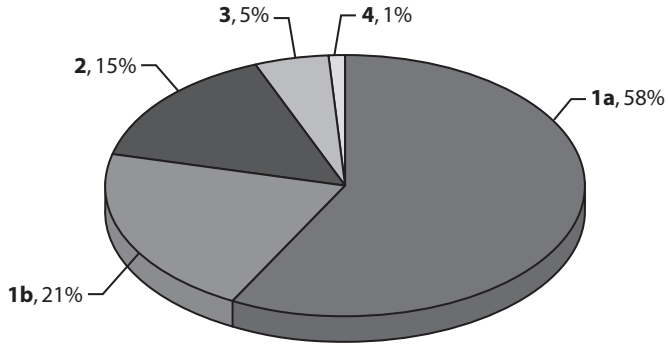


Figure 2.1. Hepatitis C virus genotype distribution in the United States

and type of medication are based on genotype, which underscores the importance of identifying genotype early.

In the United States, 70 percent of hepatitis C–infected persons are infected by genotype 1, followed by 15 percent by genotype 2, and 5 percent by genotype 3 (figure 2.1). Globally, genotypes 1/1a and 2/1b are predominant in North America, South America, and Europe. Genotype 2/1b is predominant in most Asian countries (figure 2.2). In the United States, about 50 to 60 percent of patients have genotype 1a. Types 2 and 3 genotypes are widely distributed and constitute as much as 30 percent of hepatitis C infections in some countries. Type 4 is the predominant genotype in North and Central Africa and the most common genotype in Egypt. Genotype 5 is predominant in southern Africa, and genotype 6 has been found mainly in Hong Kong. Genotypes 7, 8, and 9 have been identified only in Vietnam.

Although it has been suggested that certain genotypes (1a or 1b) may cause more severe liver disease than other genotypes, there is no firm evidence for this. The severity of liver disease depends on many factors, including immune status, alcoholism, disease duration, age, sex, and the presence of other liver disease, such as the amount of fat in the liver.

Genotype also determines the response rate to treatment. For example, genotype 1a is more difficult to treat than 1b. With rapid advances in the development of drugs for treating hepatitis C, the medications may become genotype specific, and knowing subtypes may become very

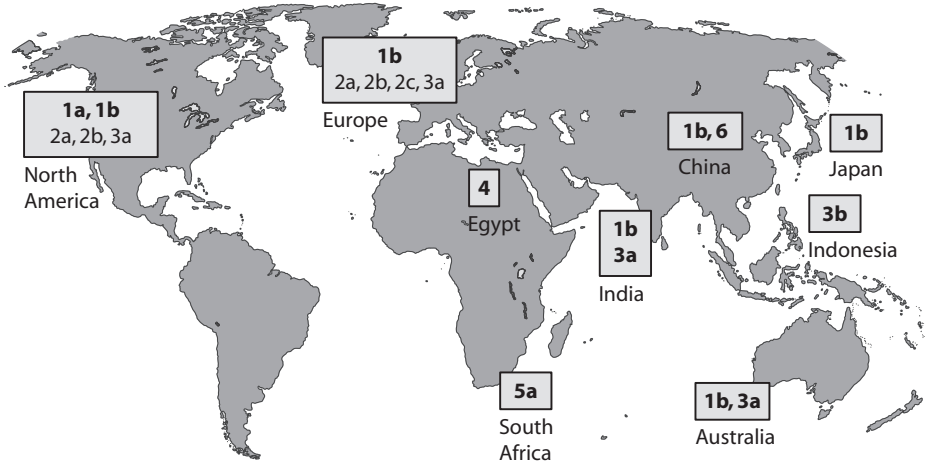


Figure 2.2. Hepatitis C virus genotype distribution worldwide (bold indicates the most common genotypes)

important before starting treatment. Once the genotype is identified, the genotype test does not need to be repeated, because genotypes do not change during the course of infection.

Liver Biopsy

A liver biopsy will determine the extent of liver injury—that is, inflammation and scarring (fibrosis) of the liver. Even in the absence of elevated liver enzymes or other abnormal liver test results, many physicians recommend a liver biopsy if hepatitis C infection is confirmed. If a liver biopsy shows significant inflammation or fibrosis, it is strongly recommended that hepatitis C treatment be started to clear the virus.

A liver biopsy may also help to rule out other diseases, such as alcoholic liver disease, autoimmune hepatitis, or hemochromatosis, a genetic disorder that causes excess iron build-up in the organs. Because hepatitis C is becoming easier to treat, routine liver biopsy may not be recommended for everyone.

You may be wondering whether you need to have another liver biopsy if you have had one done in the past. The answer depends on the situation. If a biopsy was done more than five years ago, and you either did not have hepatitis C treatment or the treatment was unsuccessful, an-

other biopsy would be helpful in monitoring the progression of the disease.

If the initial biopsy showed mild liver injury and a repeat biopsy done 5 to 10 years later showed no progression of fibrosis, it is not critical to start treatment immediately. In this situation, a physician may choose to do another biopsy in five years or may advise you to start treatment, depending on your age and philosophy. However, if there is significant disease progression, the best available treatment should be tried so as to prevent further deterioration. In the near future, physicians' attitudes may change, given the rapid progress that has been made in developing medications to easily treat hepatitis C. The biopsy may be repeated at shorter intervals for liver transplant recipients with hepatitis C infection or if the initial or subsequent biopsy showed severe inflammation or fibrosis. However, once an infected person has developed cirrhosis, or permanent severe scarring of the liver, a repeat biopsy will not provide any further information.

There are other tests that could be used instead of liver biopsy to assess the severity of liver fibrosis, but except for elastography (similar to ultrasound, and noninvasive), most tests are not reliable for accurately assessing liver fibrosis. The role of elastography to assess liver fibrosis is currently being evaluated in the United States. These tests are discussed in more detail in chapter 3.

Symptoms such as confusion, leg or abdominal swelling, or other abnormal physical signs, such as jaundice, reddened palms (palmar erythema), swollen blood vessels (spider nevi), widening of fingers (clubbing), and flapping of hands (asterixis), are seen only when liver disease is very advanced. In chapter 4, we discuss possible signs and symptoms of liver disease.

Additional Tests

To rule out other common liver diseases, a physician may decide that additional tests would be helpful. Blood counts, including hemoglobin, white cells, and platelets, are routinely done. Low platelet count (thrombocytopenia) may suggest that liver disease is advanced and the person has developed portal hypertension. A clotting test, called prothrombin

time, may be done before liver biopsy. If prothrombin time is elevated, it may indicate more severe liver disease. Depending on the situation, other blood tests requested may include thyroid function, blood sugar, alpha-fetoprotein (AFP), and cryoglobulin.

An ultrasound or computed tomography (CT) scan of the liver also may be useful for your physician to detect liver cancer and other conditions. Because liver cancer is one of the complications of hepatitis C infection, having a baseline image is helpful for future comparison. The imaging may also show the presence of fat (steatosis) and other abnormalities, such as fluid-filled spaces (cysts) or benign tumors of blood vessels (hemangiomas).

Details about these and other liver tests are provided in chapter 3.

3

Common Tests Used to Diagnose Liver Disease

A physician can diagnose liver disease by collecting information on the person's physical signs and symptoms, risk factors, and family and social history and by doing a physical examination, blood tests, radiological tests, and liver biopsy. This chapter provides some more details about diagnosing liver disease using blood tests, radiological tests, and liver biopsy, including how they are done and how to interpret the results.

Blood Tests

Because of the routine use of automated blood tests, many "healthy" individuals can have abnormal results on liver enzyme tests. Abnormalities in liver enzyme levels are often detected in healthy individuals during yearly physical examinations or insurance evaluations and sometimes during routine screening before blood donation. Many people who have hepatitis C are diagnosed during some of these routine tests. The abnormalities detected are often mild and nonspecific, but these findings may lead to expensive investigations unless the treating physician has a systematic approach to managing such findings. It is important to understand that small abnormalities in liver enzymes or other liver tests may indicate serious liver diseases. Moreover, approximately 10 percent of people may have normal liver test results despite the presence of cirrhosis. The commonly used blood tests are shown in table 3.1.

These tests, with the exception of prothrombin time, are collectively known as liver function tests, which is a misnomer because many of the

Table 3.1. Commonly Used Blood Tests for Diagnosing Liver Disease

Liver function tests
Albumin
Globulins
Bilirubin (total, direct, indirect)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Alkaline phosphatase
Gamma glutamyl transpeptidase (GGT)
Lactic dehydrogenase
Prothrombin time (PT)

Table 3.2. What Do the Test Results Mean?

Test Result	*Meaning*
Elevated aspartate aminotransferase	Liver cell injury
Elevated alanine aminotransferase	Liver cell injury
Elevated alkaline phosphatase	Bile duct injury or poor bile flow
Elevated gamma glutamyl transpeptidase	Bile duct injury, alcohol use, or other medications
Low albumin	Significant liver damage
Elevated bilirubin	Poor bile flow, bile duct obstruction, or significant liver damage
Elevated prothrombin time *or* elevated international normalized ratio	Significant liver damage, or individual is taking coumadin (blood-thinning medication)

tests do not assess liver function. Instead, these tests provide information on the type of liver injury and severity of the disease. Using a combination of the results of blood tests, evaluation of symptoms, and physical examination, a physician can further assess the severity of liver disease. Table 3.2 summarizes what the results of blood tests mean.

Liver Enzymes

The patterns of abnormalities in liver enzymes, such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma

Table 3.3. Levels of Liver Enzymes Associated with Specific Liver Diseases

Test	*Normal Values*	*Abnormal Values with Diseases*
Aspartate aminotransferase (AST), alanine aminotransferase (ALT)	0 to 30 U/L (units per liter) for men 0 to 18 U/L for women (Normal values differ among laboratories.)	1- to 20-fold increase in people who have chronic hepatitis B, hepatitis C, or autoimmune hepatitis or are taking medications 20- to 50-fold increase in people who have acute hepatitis C or severe autoimmune hepatitis C 20- to 200-fold increase in people who have acute hepatitis A or B, acetaminophen toxicity, or ischemic hepatitis
Aspartate aminotransferase : alanine aminotransferase ratio (useful in alcoholic hepatitis)	—	2- to 6-fold increase in people who have alcoholic hepatitis
Alkaline phosphatase	30 to 130 U/L (Normal values may differ among laboratories.)	1- to 2-fold increase in people who have any liver disease or are taking medications 2- to 4-fold increase in people who have primary biliary cirrhosis or primary sclerosing cholangitis or are taking medications More than 3-fold increase in people who have bile duct obstruction or intrahepatic cholestasis

glutamyl transpeptidase, help the physician to assess the type and severity of injury and possibly to make the diagnosis. For example, people who experience an overdose of acetaminophen (Tylenol) may have high aspartate aminotransferase and alanine aminotransferase levels, but the majority of people will recover without any long-term liver damage. Table 3.3 shows the normal values and the types of abnormalities that can be expected in various stages of liver disease.

Elevated aspartate aminotransferase and alanine aminotransferase levels indicate injury to the liver cells (hepatocytes). Acute liver inflammation as a result of viral hepatitis (hepatitis A, B, or C, cytomegalovirus, Epstein-Barr virus, or herpes simplex virus), alcohol, acetaminophen or other medications, and lack of adequate blood flow to the liver

(ischemia) predominantly cause this type of liver cell injury. Some of these conditions cause high levels (a 20-fold to 200-fold increase) of these enzymes in the bloodstream. Chronic injury usually leads to lower levels of enzymes (mild to 20-fold increase).

Elevated alkaline phosphatase and gamma glutamyl transpeptidase usually mean a bile duct injury (e.g., primary sclerosing cholangitis, primary biliary cirrhosis), bile duct obstruction (stones, tumor), or decreased bile flow (intrahepatic cholestasis). Alcohol use and certain medications can cause elevation of gamma glutamyl transpeptidase levels without an increase in other enzymes.

The physician can identify the nature of liver injury by observing the pattern and the levels of liver enzymes and can take a series of measurements to monitor the person's response to therapy or to assess the person's spontaneous recovery. However, the range of abnormalities in liver enzymes varies widely, and there are no rigid values that can be used to diagnose any particular disease.

Albumin, Prothrombin Time, and Bilirubin

Albumin, prothrombin time, and bilirubin predict prognosis. For example, low albumin and elevated bilirubin and prothrombin time indicate the presence of more advanced liver disease. Albumin and clotting factors are synthesized in the liver, and significant liver injury results in low albumin levels and elevated prothrombin time or a measure called the international normalized ratio (blood does not clot). Although prothrombin time or international normalized ratio (INR) may be elevated in people who have significant liver damage, whether acute or chronic, serum levels of albumin decrease only in people who have ongoing liver injury for months or years (albumin has a long half-life).

People who have cirrhosis rarely have normal levels of liver enzymes, bilirubin, and albumin. When albumin decreases and prothrombin time or INR increases in people who have cirrhosis, this indicates worsening of the cirrhosis. To best assess the severity of cirrhosis, physicians can use these test results and observe the person for symptoms or signs such as build-up of fluid in the abdomen (ascites) or loss of brain function (encephalopathy).

Bilirubin is a by-product of the red blood cell destruction that happens routinely in the body. The liver processes bilirubin, excretes it into the tiny bile ducts that join to become larger bile ducts (just as streams join to become a river), and stores it in the gallbladder, from where it is periodically released into the small intestine in response to meals (see chapter 1, figure 1.4) Bilirubin could be elevated for many reasons, including increased red cell destruction (hemolysis), incomplete or poor processing because of deficiency of certain enzymes (Gilbert's syndrome is an example), inadequate liver mass (as in liver injury or cirrhosis), bile duct injury or obstruction, or combinations of many other factors (such as infection or medications). The type of bilirubin that is elevated in people who have increased red blood cell destruction or Gilbert's syndrome is called indirect (unconjugated) bilirubin. In other situations, bilirubin is mostly direct (conjugated) or a combination of both direct and indirect.

Hepatitis A Infection

In addition to the blood tests and liver enzyme tests described above, a physician will perform several other blood tests to exclude other types of liver disease in people who have hepatitis C. Given that people who have hepatitis C can also have other liver diseases, a physician will not assume that the liver damage is caused by hepatitis C before excluding other causes of liver disease. The common tests for hepatitis A and their interpretations are shown in table 3.4.

Table 3.4. Tests for Hepatitis A Infection

Test	*Meaning of Results*
Hepatitis A IgM antibody	Presence indicates acute hepatitis A infection.
Hepatitis A IgG antibody	Presence indicates previous exposure to hepatitis A.
Hepatitis A total (IgM + IgG) antibody	Presence indicates either acute or previous infection, but indicates previous infection in people without symptoms.

For individuals who have hepatitis C or other liver diseases, having hepatitis A can be fatal, so it is important for these individuals to prevent hepatitis A infection by getting vaccinated. The hepatitis A vaccine is safe and is routinely given to children. Before vaccinating an individual, a physician will first check the person's hepatitis A IgG antibody or total antibody levels. If no antibodies are detected, the individual should take two doses of the hepatitis A vaccine, six months apart, to prevent hepatitis A infection. Most people develop life-long immunity (protection from infection) with two doses. A small number of people may never develop immunity. When people develop immunity, either from previous infection or by vaccination, the hepatitis A IgG antibody test will become positive and will remain positive. Occasionally, a person may require a booster dose of vaccine.

> People who have liver disease and are not immune to hepatitis A or B should receive vaccination for both hepatitis A and B. Please ask your doctor whether you need vaccination.

Hepatitis B Infection

Hepatitis B infection (present or previous) is common in people who have hepatitis C, because both infections are spread in similar ways. Hepatitis B is extremely infectious. The majority (90 to 95 percent) of people who have hepatitis B, if they became infected as adults, develop immunity (that is, clear the infection and become resistant to further infection). Individuals who become infected as babies (from their infected mothers) or during early childhood rarely develop immunity.

People who had a previous or have a current hepatitis B infection keep the hepatitis B DNA in their liver cells (in the cell nucleus) for the rest of their lives. The infection may get reactivated after a liver transplantation or, rarely, after chemotherapy, because the person's immune system is suppressed.

People who have had no previous hepatitis B infection should get vaccinated against hepatitis B. The hepatitis B vaccine is safe, and side effects are extremely rare. In many countries, all children are vaccinated

Table 3.5. Tests for Hepatitis B Infection

Test	*Meaning of Results*
Hepatitis B DNA	Presence indicates active viral replication.
Hepatitis B core IgM antibody	Presence indicates acute infection.
Hepatitis B core IgG antibody	Presence indicates previous or ongoing chronic infection.
Hepatitis B surface antigen	Presence indicates active infection, or person is partially immune.
Hepatitis B surface antibody	Presence indicates complete immunity by infection or vaccination.
Hepatitis B virus e antigen	Presence indicates active replication, but its absence does not indicate absence of active replication.
Hepatitis B virus e antibody	Presence does not always mean immunity; people who are negative for hepatitis B virus e antigen but with active replication will have this antibody.

routinely against hepatitis B. In the United States, hepatitis B vaccination has become routine only recently, so most adults are not immunized against hepatitis B. Because previous infection with hepatitis B is more common in people who have hepatitis C, people should be tested to verify whether they are immune. Once individuals have hepatitis B, they do not need to be vaccinated, because they have life-long immunity. People who have an active hepatitis B infection should also not be vaccinated, but they should be treated for both hepatitis B and C.

Usually, there are two types of hepatitis B infection: hepatitis B virus e antigen positive and hepatitis B virus e antigen negative. In addition, as with hepatitis C, hepatitis B has many genotypes. To understand the blood tests (serology), it is important to know the difference between hepatitis B virus e antigen positive and hepatitis B virus e antigen negative (table 3.5).

With the hepatitis B virus e antigen positive type, the hepatitis B surface antigen (a protein on the surface of the virus) is positive, hepatitis B

virus e antigen is positive, and hepatitis B virus e antibodies are absent in the presence of active viral replication (hepatitis B DNA levels are high when there is active replication).

With hepatitis B virus e antigen negative type, the hepatitis B surface antigen is positive, but the hepatitis B virus e antigen is absent (the mutation prevents secretion of hepatitis B virus e antigen into the blood from the liver cells), and hepatitis B virus e antibodies are present despite active viral replication. Because this pattern is also seen in the hepatitis B virus e antigen positive type when the person develops immunity, even some physicians may be confused when they see the blood test results for hepatitis B.

Hepatitis B surface antibodies are present when a person develops immunity after vaccination, but hepatitis B core IgG antibody is absent after the person has been vaccinated. Both hepatitis B surface antibody and hepatitis B core IgG antibody are present when a person develops immunity after a previous infection.

For individuals who have hepatitis B virus e antigen, the purpose of treatment is to prevent replication of the virus and convert positive hepatitis B virus e antigen to positive hepatitis B virus e antibody status (hepatitis B virus e antigen becomes negative when antibodies appear). For individuals who have active liver disease and are hepatitis B virus e antigen negative, there are no tests to determine when to stop treatment, and most physicians will consider providing treatment for the rest of the person's life or until the hepatitis B surface antigens disappear.

Other Blood Tests

Other blood tests that the physician commonly uses to identify the nature of liver injury include anti-nuclear antibodies, anti–smooth muscle antibody, anti-mitochondrial antibody, globulins, ferritin, iron saturation, alpha-1-antitrypsin phenotype, 24-hour urine copper, ceruloplasmin, and alpha-fetoprotein. Table 3.6 shows the relevance of some of these tests.

Hemochromatosis gene analysis is a useful tool for people who are suspected to have hemochromatosis, and it could be used to screen family

Table 3.6. Other Tests Used for Diagnosis of Liver Disease

Test	*Relevance*
Immunoglobulins	High levels may indicate immune-mediated liver disease.
Anti-nuclear antibody	Immune-mediated liver disease, such as autoimmune hepatitis, may be suspected if levels are above 1/160.
Anti–smooth muscle antibody	Immune-mediated liver disease, such as autoimmune hepatitis, may be suspected if levels are above 1/80.
Anti-mitochondrial antibody	Presence suggests primary biliary cirrhosis if levels are more than 1/40.
Ferritin	High levels occur in people who have acute hepatitis or genetic iron overload (hemochromatosis).
Iron saturation	High saturation (especially fasting) may be suspicious for hemochromatosis.
Alpha-fetoprotein (normally less than 10 IU/ml)	Elevated levels occur in people who may have liver cancer; above 400 IU/ml, almost definite cancer.

members of people who have confirmed hemochromatosis with an identified gene mutation.

Radiological Tests

The radiological tests commonly used to check for liver disease include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangio-pancreatography, endoscopic retrograde cholangio-pancreatography, percutaneous transhepatic cholangiography, and angiogram.

Ultrasound, CT, or MRI is used to assess liver tissue (parenchyma) for fat, tumors, or cirrhosis and to see whether blood vessels are open (patent). These tests are regularly used for people who have hepatitis C cirrhosis, to look for possible liver cancer. When a CT scan is performed to

look for a tumor, the person is given a contrast agent intravenously, and scans are done in arterial and venous phases (rapid and late sequences, helical CT). Similarly, contrast agents are given when an MRI is to be performed, to increase the test's sensitivity. It is extremely important to get these tests done and interpreted by radiologists with an interest in liver tumors. Otherwise, the physician may not detect a small cancer when it is most likely to be curable. In the author's experience, many CT and MRI scans used to screen for liver tumors are inadequate for this purpose.

Magnetic resonance cholangio-pancreatography, endoscopic retrograde cholangio-pancreatography, or percutaneous transhepatic cholangiography is done to look at the bile ducts, if bile duct disease or obstruction is suspected.

An angiogram is a radiological test used to visualize an artery and, sometimes, veins (delayed images). A contrast agent is injected selectively into a blood vessel of interest. Depending on the vessel, catheterization of a major blood vessel is necessary to perform these tests.

Liver Biopsy

Physicians perform a liver biopsy to confirm liver disease in people who are suspected to have cirrhosis. In people who have hepatitis C infection, examination of a liver biopsy sample by a pathologist, after appropriate staining of the sample (liver histology), will establish the severity of inflammation (grade) and level of fibrosis (stage). People who have moderate or severe inflammation have a high likelihood of developing cirrhosis. More importantly, the severity of the fibrosis predicts when it is likely to progress to cirrhosis. Having a biopsy will also establish whether the person suffers from any other type of liver disease.

During a liver biopsy, the physician first injects the skin with an anesthetic (lidocaine) and then passes a needle between the ribs (figure 3.1). The physician usually performs the biopsy under ultrasound localization or guidance. Complications are rare (less than 1 in 2,000) after a liver biopsy. Possible complications include bleeding, perforation of an organ close to the liver (colon, gallbladder, lungs), pain, or infection. Because

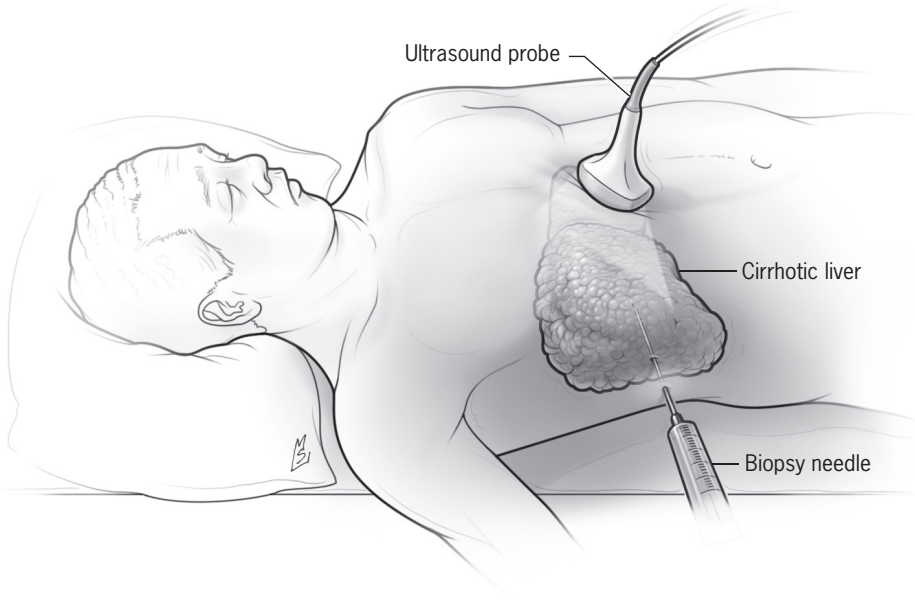


Figure 3.1. A liver biopsy

these complications are extremely rare, most physicians would consider the benefits of a liver biopsy to far outweigh the risks.

Before the liver biopsy can be performed, the physician will conduct clotting tests (prothrombin time, platelets). The person's platelet count should be more than 50,000, and prothrombin time should not be prolonged for more than 3 to 4 seconds (or INR should be less than 1.6) above the normal range. If clotting tests are unsatisfactory, the biopsy may be done by other means, such as transjugular liver biopsy, in which an interventional radiologist passes a catheter through the neck vein and gets a liver biopsy sample using a special needle. People should not take aspirin or similar medications (ibuprofen or other nonsteroidal anti-inflammatory drugs) for one week before the biopsy and for 48 to 72 hours afterward. These drugs increase the risk of bleeding because of their effects on platelets.

A series of liver biopsies (three to five years apart) may help the physician predict the progression of liver disease in a person who has hepatitis C. These biopsies are especially beneficial if the person decides not

to opt for treatment or did not respond to treatment. If serial biopsies do not show disease progression, the person will find it reassuring and may choose not to have treatment (this strategy is not advised, however, since current treatments are very effective). On the contrary, if there is marked progression, treatment should not be delayed.

In people who have received a liver transplant and have hepatitis C infection, liver disease may progress rapidly to cirrhosis because of medications that suppress their immune systems, and for these individuals, yearly protocol biopsies may help to assess progression of the disease. Even in this group, most people could be cured with the current treatment.

If the physician finds a suspicious area (for example, a liver tumor) on any radiological tests, unless a firm diagnosis can be made without liver biopsy, the physician will usually perform an ultrasound-guided (or CT-guided) biopsy of the suspected area. This biopsy is especially important if liver cancer is suspected. However, if the alpha-fetoprotein level is higher than 400 IU, a biopsy is not necessary, because an increase in alpha-fetoprotein to more than 400 IU indicates liver cancer (hepatocellular cancer or hepatoma) in people who have cirrhosis. Similarly, if the tumor shows characteristic features of liver cancer on CT scan or MRI, biopsy of the tumor is not necessary.

Other Tests

Because liver biopsy is an invasive procedure, other tests are being developed to assess the severity of scarring (fibrosis) (table 3.7). The most commonly used blood test is FibroSURE, which uses a combination of

Table 3.7. Accuracy of Noninvasive Tests Used to Assess Fibrosis

Test	*Accuracy*
AST:ALT ratio	60% to 70%
AST / platelet count	70% to 80%
FibroSURE	75% to 85%
FibroMeter	80% to 85%

biochemical markers to assess the severity of fibrosis. Although FibroSURE is widely used, it cannot adequately distinguish intermediate stages of fibrosis reliably and consistently.

Elastography (FibroScan), another type of test, has an ultrasound-like device that measures fibrosis, and this method may become more widely used in the future to assess fibrosis. Although this test is more reliable (80 to 90 percent) than blood tests in assessing fibrosis, obesity is a limiting factor. Like blood tests, it can be used to diagnose cirrhosis more accurately, but moderate fibrosis cannot be accurately assessed. As a noninvasive test, it can be used repeatedly over a long period of time to assess the progression of fibrosis, and it may be used more routinely in the future.

Common Patterns of Liver Test Abnormalities

Individuals' abnormal liver test results can be classified into several categories based on the pattern of elevated liver enzymes and the severity. This arbitrary classification, despite the overlap between groups, is often useful for the physician in discussing possible strategies to diagnose the condition and assess the person's prognosis. The classifications are

- People who have no symptoms and have hyperbilirubinemia
- People who have marginally abnormal aspartate aminotransferase or alanine aminotransferase levels
- Individuals who have only elevated alkaline phosphatase levels
- People who have no symptoms but have abnormal blood tests
- Individuals who have jaundice and who have, predominantly, elevated alkaline phosphatase
- People who have acute hepatitis and have symptoms

In general, most physicians can make a diagnosis of liver disease by observing the patterns of liver enzymes and doing a minimal number of investigations. It is extremely important not to disregard abnormal liver test results because many liver diseases are treatable in their early stages. Having no symptoms or no marked changes in liver enzymes does not

exclude serious liver disease. Individuals who have any doubts about the diagnosis should get a second opinion from an experienced liver specialist (hepatologist).

> Elevated liver enzymes, even if the elevation is minimal, should be investigated by an experienced physician. Absence of an elevation in liver enzymes does not rule out liver disease; 10 percent of people with cirrhosis, and many people with hepatitis C or B, may have normal results on liver enzyme tests. Ask your doctor whether you should have tests for hepatitis C or B.

4

Signs, Symptoms, and Complications of Liver Disease

The symptoms and physical signs of all types of liver disease are similar, whether caused by hepatitis C or other conditions. Symptoms are what a person experiences (for example, nausea or itching); signs are physical findings on examination by a physician (such as jaundice or enlargement of the liver). This chapter describes the common symptoms and signs, as well as some of the complications, of liver disease. The complications of scarring (cirrhosis) are discussed in more detail in chapter 8.

Signs and Symptoms

Most people who have an acute hepatitis C infection do not experience any symptoms. Therefore, they may not know for many years that they have hepatitis C, unless the disease is detected during a routine blood donation screening or by abnormal liver test results during a routine physical.

If an acute hepatitis C infection is severe, some people can develop general (nonspecific) symptoms, such as loss of taste, poor appetite, nausea, and fatigue. Jaundice, dark urine, and itching (pruritus) are other symptoms. Occasionally, people may also develop right upper quadrant discomfort or pain. Table 4.1 lists the most common general symptoms that affect people who have an acute hepatitis C infection, as well as symptoms that may indicate other liver conditions.

If people experience pain as a predominant symptom, it is more likely that the problem is not related to liver disease. For example, if a person

Table 4.1. Symptoms of Liver Disease and Potential Causes

Symptoms	*Possible Cause*
Poor appetite Loss of taste Nausea Right upper quadrant discomfort or pain Jaundice Dark urine Itching	Acute hepatitis (inflammation of liver)
Jaundice Severe right upper quadrant pain, especially after meals	Bile duct obstruction due to gallstones
Painless jaundice Weight loss Age older than 50 years	Cancer of pancreas, gallbladder, or bile ducts
Jaundice Fluid in legs Swelling of abdomen (ascites) Memory loss	Scarring of the liver (cirrhosis)

has jaundice and severe pain after meals, this may be due to a bile duct obstruction because of gallstones. Elderly people who have a sudden onset of painless jaundice may have pancreatic or bile duct cancer.

During the early stages of chronic liver disease, including chronic hepatitis C, symptoms are rare. In general, people develop symptoms only during the advanced stages of liver disease, so it is important for people who have chronic hepatitis C to seek help before they develop symptoms. Sometimes, people will refuse hepatitis C treatment because they do not have any symptoms; this strategy is not helpful in managing the disease.

Nonspecific symptoms such as fatigue and mild right upper quadrant discomfort can occur in people who have chronic liver disease. The symptoms listed in table 4.2 indicate that the liver disease may have progressed to advanced scarring (cirrhosis).

None of these symptoms are exclusive to liver disease. For example, some pregnant women have redness of palms and some spiderlike collections of blood vessels that appear as red spots with "spidery legs" that turn white with pressure. These spots may be related to estrogen that is

usually cleared by the liver (which is why pregnant women may develop this sign). Individuals who have any of these symptoms should consult a physician before coming to any conclusions.

As disease progresses, people may notice swelling in the legs (called pitting edema) and abdominal distension (called ascites). Some of the serious signs of liver disease (ascites, bleeding, and confusion) are explained in more detail in chapter 8.

Fatigue and Depression

People who have liver disease, especially hepatitis C infection, often experience fatigue and depression. It is difficult to know whether these symptoms are more common in people who have mild hepatitis C infection, or whether they are precipitated by other factors, including the fear of having a serious disease. In one study, when blood donors who had hepatitis C were evaluated, approximately 65 percent complained of fatigue. However, 70 percent of blood donors who did not have hepatitis C also complained of fatigue, indicating that fatigue is a common symptom in the general population. Some studies show that people who have hepatitis C experience an improvement in fatigue after clearance of the virus by treatment.

Some people complain of depression and mental impairment, such as confusion, but there are conflicting reports regarding these symptoms.

Table 4.2. Symptoms and Signs of Advanced Liver Disease

Symptoms	*Signs*
Severe fatigue	Spider-like collections of blood vessels (spider nevi) on face, arms, or chest
Short-term memory problems	Loss of armpit or pubic hair
Jaundice	Redness (erythema) of palms
Impotence in men	Decrease in size of testicles
Enlarged breasts in men (gynecomastia)	Prominent veins on the abdominal wall
Abdominal or leg swelling	Fluid in the abdomen (ascites)
Vomiting blood or passing black stool	Flapping tremors (asterixis)
	Wasting of muscles

Some psychiatric problems, including depression, posttraumatic stress disorder, and psychosis, occur slightly more often in some people who have hepatitis C, including Vietnam War veterans. Also, because many people who have hepatitis C infection also have a previous history of drug abuse or alcoholism, separating the consequences of these habits from the psychological effects of hepatitis C can be difficult.

Similarly, some studies show an increase in mental impairment, such as loss of memory and ability to concentrate, among people who have hepatitis C. In autopsy results, the hepatitis C virus has been found in the brain, and some researchers suggest that hepatitis C may result in the immune system damaging the brain, which may cause these mental problems. Alternatively, hepatitis C may stimulate natural chemicals formed in the body (called cytokines) that may influence serotonin (a neurotransmitter) metabolism, causing depression and other problems. This area of research is active and continues to yield new information. Currently, the role of hepatitis C infection in depression and other psychiatric problems is still not known.

Complications of Cirrhosis

Cirrhosis, or advanced scarring of the liver, can occur after many years in people who have liver disease or injury. If the cirrhosis is diagnosed early and its cause is treated, the damage may be reversed.

As cirrhosis progresses and more scar tissue forms, the liver cannot carry out all of its functions, resulting in serious complications, including fluid accumulation in the abdomen and legs, confusion, and bleeding from the stomach or esophagus. When these complications occur in people who had previously stable liver disease, it is described as "decompensation of liver disease." Most of the complications arise because of an increase in portal vein pressure, or portal hypertension (see chapter 8 for more information).

The complications of cirrhosis include the following:

- Fluid accumulation in the body:
  - In the abdomen (ascites)

  - In the legs, with swelling (pedal edema)
  - Generalized (anasarca)
- Bacterial infections:
  - Infection of fluid in the abdomen (spontaneous bacterial peritonitis)
  - Recurrent urinary tract infections
  - Chest infections
- Bleeding from the gastrointestinal tract:
  - Bleeding in the esophagus (esophageal varices)
  - Bleeding in the stomach (gastric varices) or from the lining of the stomach (portal hypertensive gastropathy)
  - Bleeding in the colon and other areas (ectopic varices)
- Cognitive or memory problems (hepatic encephalopathy):
  - Change in sleep pattern
  - Short-term memory loss
  - Confusion
  - Coma (rare)
- Kidney failure (hepatorenal syndrome)
- Liver cancer (hepatocellular cancer or hepatoma)

Ascites, Edema, and Bacterial Peritonitis

Fluid in the abdomen (ascites) is a major complication of cirrhosis and may be accompanied by swelling of the legs (edema). Initially, ascites does not cause any discomfort, but it may be bothersome to people because of its cosmetic appearance. However, as ascites gets worse and becomes tense, it may cause significant discomfort and, at times, pain. Tense ascites also may cause breathing difficulty. Rarely, tense ascites causes an umbilical hernia to burst. The fluid in the abdomen may also get infected, which is a serious complication that may lead to kidney failure. The treatment of ascites is discussed in more detail in chapter 8.

Bleeding from the Gastrointestinal Tract

People who have cirrhosis are at risk of bleeding from the gastrointestinal tract because, when the pressure in the portal vein of the liver increases, collateral blood vessels develop to reduce that pressure. Some

of these veins, called varices, travel along the lining of the gastrointestinal tract. Most commonly, these varices are seen in the stomach and esophagus. Sometimes, these varices may rupture and cause major bleeding.

Bleeding from the gastrointestinal tract is an unpredictable complication of cirrhosis. Bleeding can also occur at other sites, such as different parts of the small and large intestine, but this is rare. The risk of death is 20 to 50 percent with each bleeding episode, depending on the severity of liver disease. Approximately one-third of all deaths in people who have cirrhosis can be directly attributed to acute variceal bleeding.

Individuals who have cirrhosis should immediately go to the hospital if they have any signs of bleeding (red or black stool, vomit containing blood, or significant dizziness). Early intervention improves the chances of recovery.

The risk of rebleeding is substantial after one episode of bleeding. Therefore, it is important for people to follow the physician's instructions when they are discharged from the hospital.

Hepatic Encephalopathy

As cirrhosis progresses, people may develop memory problems and, in later stages, confusion. These symptoms are collectively diagnosed as hepatic encephalopathy. The symptoms are caused by toxins that are not removed by the liver. Typically, ammonia and other toxins from the intestine are processed by the liver. For people who have cirrhosis, this process may not happen, either because of poor liver function or because of shunting of blood through collaterals (blood vessels that bypass the liver). As a result, these toxins may reach the brain, causing a variety of symptoms including sleep disturbances (reversal of sleep pattern), memory problems, confusion, and, in extreme cases, coma. The treatment of hepatic encephalopathy is also discussed in more detail in chapter 8.

Other Serious Complications

Advanced liver disease may also cause damage to other organs. Kidney failure (hepatorenal syndrome), which is one of the most serious com-

plications of advanced cirrhosis, is caused by the increased blood pressure in the portal vein and decreased blood flow to the kidney.

Rarely (in less than 5 percent of cases of cirrhosis), people with liver disease and portal high blood pressure may develop lung complications, including shortness of breath, inadequate oxygenation of the blood (because blood is bypassing the lungs, a condition known as hepatopulmonary syndrome), or increased pressure in the pulmonary artery (porto-pulmonary hypertension).

Advanced liver disease may also cause a type of heart failure known as cirrhotic cardiomyopathy ("cardiomyopathy" is a general term used for diseases of the heart muscle). This condition is extremely rare.

Advanced cirrhosis sometimes causes muscle wasting, malnutrition, deficiency of trace metals and vitamins, and bone disease (osteopenia and osteoporosis).

> Liver cancer is a serious complication of cirrhosis. People with hepatitis B (even in the absence of liver disease) and anyone with advanced fibrosis or cirrhosis (irrespective of the cause) should have liver scans (ultrasound, CT, or MRI) every 6 to 12 months.

Another serious and common complication of cirrhosis is liver cancer. People who have hepatitis C may develop liver cancer if they have advanced fibrosis. People who have hepatitis B and do not have any fibrosis may also develop liver cancer, because the hepatitis B virus is a cancer-causing virus.

- Symptoms are rare in early stages of liver diseases.
- When symptoms occur, this is an indication of advanced liver disease; people should not wait to develop symptoms if they believe they may have any liver disease, including hepatitis C.
- Early intervention will improve the outcome of liver disease, and, ideally, a liver specialist (hepatologist) should be consulted for optimal management. Most of these complications can be managed effectively.

5

Acute Hepatitis C

An understanding of both the relationship between and the distinction between the acute and chronic phases of hepatitis C is essential. In chapter 1, we noted that acute hepatitis C is a short-term illness that occurs within the first six months after exposure to the hepatitis C virus. For about 70 percent of people who have hepatitis C, acute infection leads to chronic infection. For people who have chronic hepatitis C, the virus remains in their bodies and causes long-term illnesses that can lead to serious liver problems, including liver damage, cirrhosis, liver failure, or liver cancer. Because most people who have an acute infection develop chronic hepatitis C, most of this book focuses on chronic hepatitis C and its signs and symptoms, testing, current treatment options, potential complications, and the positive outlook for its treatment in the future. In this chapter, we focus on acute hepatitis C infection.

Acute hepatitis C infection may occur 2 to 12 weeks from the time of exposure (on average, 7 weeks), and illness from the infection may last for 2 to 12 weeks. Acute hepatitis can be mild—only about 10 to 20 percent of people who have the infection will develop symptoms. Or the acute infection can be severe and prolonged (weeks to months), with jaundice or liver failure, but it rarely causes the sudden onset of liver failure (a condition called acute liver failure) unless the person has previous liver disease.

The hepatitis C virus is the cause of 15 percent of all acute hepatitis cases reported in the United States. Other common causes of acute hepatitis include medications (acetaminophen being the most common),

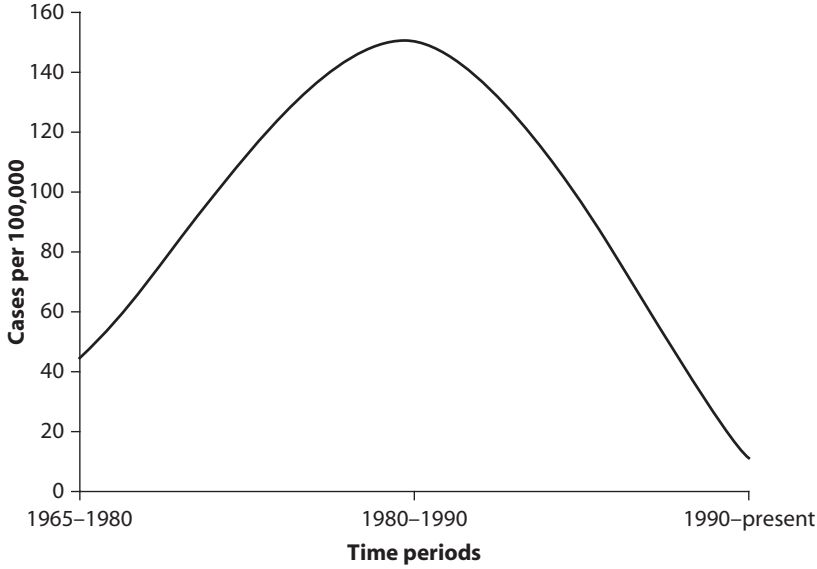


Figure 5.1. Incidence of new cases of hepatitis C in the United States. The incidence has decreased since 1980.

hepatitis A or hepatitis B viruses, and autoimmune hepatitis. For between 15 and 20 percent of people, the cause of infection is not identified and is thought to be possibly an unidentified viral infection. The number of new hepatitis C infections has decreased significantly over the past three decades in the United States (figure 5.1).

Identifying the infection early may lead to more effective cure and treatment strategies. The cure rate is higher when the infected person is treated within six months of acquiring the infection. Table 5.1 summarizes some general properties of acute hepatitis C infection.

Symptoms

The term *acute* refers to the sudden onset and short length (course) of infection—usually occurring within the first six months after exposure—rather than to the severity of the disease or to its symptoms. In fact, most people (80 to 90 percent) who have acute hepatitis C infection do not develop symptoms. When symptoms appear, they are often vague and

Table 5.1. Characteristics of Acute Hepatitis C in the United States

An estimated 38,000 people acquire a hepatitis C infection every year.
Approximately 10% to 20% of people who have acute hepatitis C develop symptoms.
The hepatitis C virus causes 15% of acute hepatitis cases.
People who have acute hepatitis C and develop jaundice are likely to spontaneously "clear" the infection.
Treatment is highly effective for people who have an acute hepatitis C infection.

Table 5.2. Symptoms of Acute Hepatitis C in a Study Population

Symptoms (present in only 10% to 20% of participants)	*Proportion of the Participants with Symptoms*
Jaundice	71%
Flulike illness	64%
Dark urine and pale stool	36%
Nausea or vomiting	35%
Abdominal pain	26%

nonspecific, such as loss of taste, poor appetite, nausea, fatigue, and occasionally, right upper quadrant discomfort or pain. Other more specific symptoms can be jaundice, dark urine, and itching (pruritus). If pain is the predominant symptom, however, it is unlikely to be related to liver disease. Jaundice occurs in approximately 10 to 20 percent of acute infections. Most acute infections are not diagnosed, and the infection is diagnosed only later in routine testing or because of abnormal levels of liver enzymes.

Because acute hepatitis C is not encountered often, there is only a limited number of studies that have looked at symptoms associated with acute hepatitis C infection. In a study in which 16 percent of the study participants had symptoms (table 5.2), jaundice was the most common symptom, followed by flulike illness, dark urine and clay-colored stools, nausea or vomiting, and right-side abdominal pain.

According to the Centers for Disease Control and Prevention, between 15 and 25 percent (higher if jaundice develops) of people who have acute

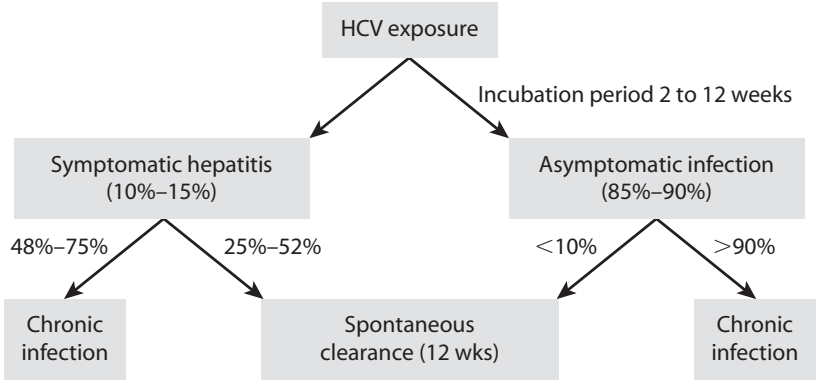


Figure 5.2. Natural outcomes of infection by the hepatitis C virus (HCV)

hepatitis C "clear" the virus without treatment (figure 5.2). When people clear the virus, their immune systems have eliminated all the viral particles and destroyed all the hepatitis C–infected cells. These people will have hepatitis C antibodies in their blood for the rest of their life, but they have no hepatitis C virus in their body. However, the presence of antibodies does not protect these people from future reinfection by the hepatitis C virus.

People who develop jaundice have a higher rate of spontaneous clearance of hepatitis C infection than people who have an infection without symptoms. When a person has jaundice, it may indicate that the infected person has an effective immune response to the virus. Other factors that have been associated with spontaneous clearance include the presence of flulike symptoms, low peak viral load (low levels of hepatitis C RNA), and being Caucasian.

Diagnosis

Because there are no blood tests that can distinguish between a person who has an acute hepatitis C infection and someone who has had the infection for a long time (chronic infection), no definitive tests are available to diagnose acute hepatitis C infection. A physician may suspect a person has an acute hepatitis C infection under the following circumstances:

- The person has had an identifiable exposure to the virus, followed by an increase in enzymes or the presence of symptoms.
- The person has had consistently normal liver enzymes, followed by a marked increase in enzymes and the presence of symptoms.
- The person had an earlier negative hepatitis C RNA test result, but a second test result is positive. (This is not a routine test, so it is unlikely that the test would be performed unless the physician suspected the person had hepatitis C infection.)

A large increase in alanine aminotransferase levels may represent an acute exacerbation of chronic hepatitis C infection or a different acute process, such as alcoholic hepatitis, that occurs in addition to the chronic hepatitis C infection.

The only way for the physician to conclusively diagnose acute hepatitis C infections is to record the development of antibodies (called seroconversion) in an individual who previously lacked antibodies (that is, was seronegative). This process happens most frequently when a needle-stick exposure occurs and the exposed individual is monitored for a certain time, or in studies that look at high-risk individuals who are negative for hepatitis C infection. However, testing for hepatitis C antibodies is not a reliable way to confirm an acute hepatitis C infection because in as many as 30 percent of people, the production of antibodies may be delayed when symptoms appear. In addition, anyone who is immune-compromised may not be capable of mounting an effective antibody response. And research has shown that some people who successfully clear the virus may not produce any antibodies or may have rapid antibody loss. A person may develop antibodies to the hepatitis C virus only after being infected for many weeks. In addition, up to 10 percent of people who have the infection will lose hepatitis C antibody markers after they have completely recovered from an acute infection.

The patterns of immune antibody response with acute hepatitis C infection are illustrated in figure 5.3 (for people with successful treatment or spontaneous resolution) and figure 5.4 (for chronic infection).

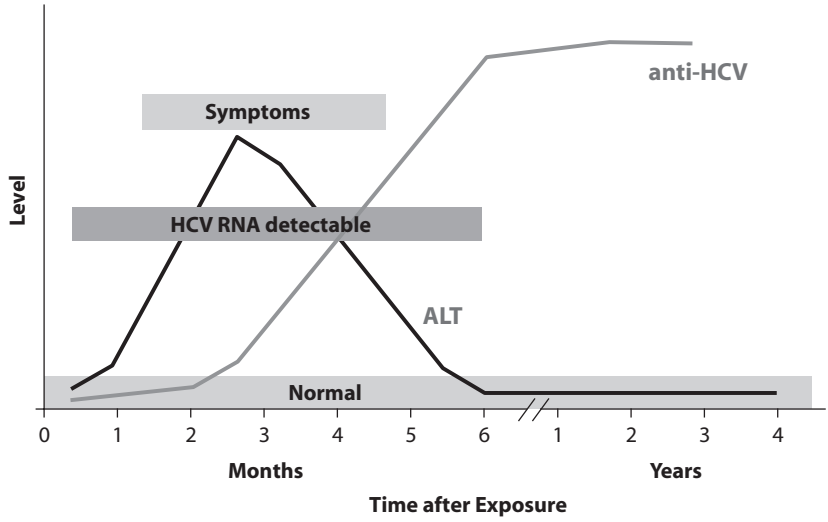


Figure 5.3. Blood test pattern (alanine aminotransferase [ALT] and viral antibody) in acute hepatitis C virus (HCV) infection with complete recovery (with or without treatment)

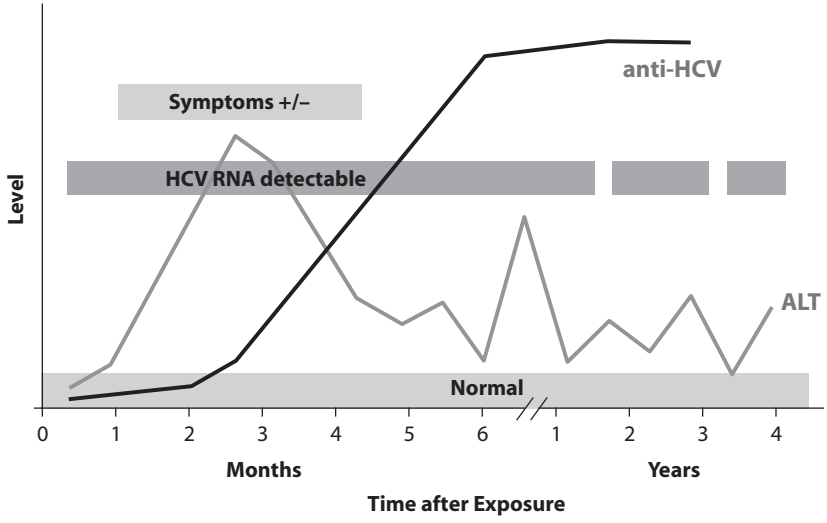


Figure 5.4. Blood test pattern (alanine aminotransferase [ALT] and viral antibody) in acute hepatitis C virus (HCV) infection with progression to chronic infection

Although antibody tests are not useful in diagnosing acute hepatitis C infection, these tests can effectively diagnose acute hepatitis A or hepatitis B infections. Soon after an acute hepatitis A or B infection starts, a type of immunoglobulin antibody called IgM appears, and then as IgM antibodies disappear from the blood, IgG antibodies appear. However, for a person with hepatitis C, IgM antibody levels remain relatively constant in both acute and chronic infections, so measuring IgM antibodies is not useful in diagnosing an acute hepatitis C infection.

The preferred method of diagnosing an acute hepatitis C infection is to detect hepatitis C RNA, using reverse transcriptase–polymerase chain reaction (PCR). If a person's blood is tested immediately after an acute infection, the hepatitis C virus antibodies may be absent, but the results of the PCR test for the viral RNA will be positive.

Management of Accidental Exposure

Accidental exposure typically happens to healthcare workers, mainly by needle-stick injuries, and carries a less than 2 percent risk of hepatitis C transmission. Dealing with this type of exposure is difficult because there are no clear guidelines and a lack of data. Treatment recommendations are summarized in table 5.3. An exposed individual who has a confirmed infection may not be willing to wait the recommended three months before starting treatment, but approximately one-half of exposed individuals may clear the virus spontaneously, especially if they develop symp-

Table 5.3. What Should You Do after an Accidental Exposure to Hepatitis C?

Report the incident (needle-stick injury, splash of blood or body fluids) immediately to the local authority for an assessment of the risk of infection; provide the necessary information about the person involved.
Have hepatitis C RNA checked at the time of exposure and at 1 month, 3 months, and 6 months after exposure.
Take treatment if hepatitis C RNA test becomes positive.
Delay treatment (at least 3 to 4 months) if you have symptoms, because spontaneous clearance is likely.

toms. Because people who do not have symptoms have little chance of spontaneously clearing the virus, once the infection is confirmed with a PCR test, these people should immediately consider antiviral therapy.

There is no evidence to suggest that antiviral treatment immediately after exposure (without any evidence of transmission) is beneficial. Most physicians agree that it is best to continue monitoring the exposed person by testing for hepatitis C RNA for three to six months after exposure.

Treatment

As previously mentioned, approximately 15 to 25 percent of individuals who have acute hepatitis C infection will spontaneously clear the virus and require no treatment. In contrast to treatment for chronic hepatitis C, there have been no large clinical trials to guide the treatment of people who have acute hepatitis C infection. However, there is an increasing amount of evidence to suggest that the response rate is high for people receiving treatment for acute hepatitis C. Data from various studies suggest that people who have acute hepatitis C can have a higher clearance rate if they have three to six months of treatment with a combination of interferon and ribavirin (see chapter 13 for more information about these treatments). Data from 17 studies examining acute hepatitis C treatment showed a strong trend favoring people who were given medication compared with people who were not (that is, a control group). The treated individuals had an average cure rate of 62 percent (range, 37 to 100 percent), compared with the untreated individuals' average cure rate of 12 percent (range, 0 to 20 percent), which was a statistically significant difference. The studies included in this comparison differed in many ways, including participant characteristics and the type, dose, and duration of medication given. However, overall, the data support the benefit of using interferon to reduce the possibility that people who have acute hepatitis C will develop a chronic hepatitis C infection.

In addition, some studies of acute hepatitis C treatment that did not include a comparative group that received no treatment (that is,

uncontrolled studies) reported encouraging results demonstrating a cure rate ranging between 83 and 98 percent with antiviral treatment. Other studies reported a spontaneous viral clearance rate of 44 to 67 percent in people who had acute hepatitis C with symptoms (usually, people who developed jaundice). Therefore, it is important to assess the results of the uncontrolled studies from this perspective. Spontaneous viral clearance is rare in people who have no symptoms or jaundice.

In one study, all individuals who showed spontaneous clearance had undetectable hepatitis C RNA levels by four months from the time when symptoms first appeared. In the same study, 20 individuals began antiviral therapy three to six months after symptoms first appeared, and of these, 16 (80 percent) showed a favorable response to the treatment. Despite the varied treatment regimens (some used only interferon and others used interferon in combination with ribavirin), this study illustrates that people can have good responses to treatment with antiviral therapy given early in the chronic phase of hepatitis C infection. This strategy would avoid the unnecessary treatment of people who are likely to undergo spontaneous viral clearance. Because people who have symptoms have high rates of spontaneous clearance and excellent response rates early in the course of chronic infection, it may be best for physicians to wait for three to four months before starting antiviral therapy for these individuals.

Table 5.4 summarizes the factors to consider in deciding on treatment.

Although evidence suggests that interferon may be effective in treating acute hepatitis C, the optimal dose and type of interferon that should be used have not been determined. Based on the experience from treating people who have chronic hepatitis C, pegylated interferon (a longer-acting form of interferon) in combination with ribavirin was, until recently, the best option for treatment. Most physicians would treat acute hepatitis C for six months regardless of the virus genotype.

Although there have been no trials so far, interferon-free regimens will become the standard of care for both acute and chronic hepatitis C infections, and the treatment duration may also become shorter (8 to 12 weeks; see chapter 16). Recently, the U.S. Food and Drug Administra-

Table 5.4. Should You Receive Treatment If You Develop Acute Hepatitis C?

Increasing evidence suggests that the response rate to antiviral treatment is high for people who have acute hepatitis C.
The optimal duration of treatment is unclear, but having a shorter course of treatment (3 to 6 months) may be adequate; longer courses may be necessary if you experience a relapse.
There are no controlled trials of treatment for acute hepatitis C. Previous studies were done with pegylated interferon and ribavirin, but interferon-free treatment will become the standard of care.
Although there are no studies so far, interferon-free treatment (currently available) for 8 to 12 weeks is likely to cure more than 90% of people who have acute hepatitis C.

tion (FDA) approved oral medications, including sofosbuvir (Sovaldi), a potent medication that has minimal side effects and low risk of resistance. Although not studied to date (it may be tested soon in clinical trials), a combination of sofosbuvir and ribavirin may cure almost all people who have acute hepatitis C; both drugs are already approved by the FDA, but not for acute hepatitis C. Sofosbuvir in combination with ledipasvir (Harvoni) was recently approved by the FDA for treating chronic hepatitis C, genotype 1. This combination could also be used to treat acute hepatitis C, genotype 1. These medications and other treatment options (VIEKIRA PAK, with or without ribavirin, from AbbVie) are discussed in detail in chapter 16.

- Between 10 and 20 percent of people who have acute hepatitis C develop symptoms, so acute hepatitis C can often be overlooked.
- People who have symptoms are more likely to spontaneously clear the virus, so they can wait to make a decision about starting antiviral therapy for three months from when symptoms appear.
- If people do not have symptoms, they should consider treatment as soon as they are diagnosed, because they will probably not spontaneously clear the virus.
- Antiviral treatment using interferon alone or in combination with ribavirin has been effective in achieving cure rates of more than

80 percent. Therapy is generally recommended for 6 months, rather than 12 months, for people who have acute hepatitis C.

- Interferon-free treatment (without interferon; this treatment is currently available) for 8 to 12 weeks will become the standard of care in the near future, and these regimens may cure almost everyone who has acute hepatitis C.

6

Chronic Hepatitis C

Seventy percent of people who have an acute hepatitis C infection develop chronic hepatitis C. The conventional definition of chronic hepatitis C is the persistence of hepatitis for six months or longer. This chapter describes the symptoms, physical findings, and different stages (severity of scarring or fibrosis) of the progression of chronic hepatitis C, as well as the effects of alcohol on the disease.

Spontaneous Clearance

Once chronic disease develops, the likelihood that the person will spontaneously clear the virus is less than 10 percent. There are certain factors that may predict whether individuals with hepatitis C can spontaneously clear the virus. Spontaneous clearance is more likely in individuals who have symptoms and in women, young people, and non-alcoholics. Certain individuals have a low rate of spontaneous clearance, including those who also have HIV, are immunosuppressed for other reasons (such as having received a liver transplant and/or on immunosuppression regimens), or have minor variations in hepatitis C virus genotype.

Physical Findings and Symptoms

Although between 10 and 20 percent of people who have acute hepatitis C may have symptoms, individuals who have early chronic liver disease,

including chronic hepatitis C, rarely have symptoms. In the early stages of chronic hepatitis C, people can experience nonspecific symptoms such as fatigue and mild right upper abdominal discomfort. More often, it is people in the advanced stages of liver disease who develop symptoms, such as jaundice, fluid in the abdomen or swelling in the legs, or confusion, which is an important reason for individuals who have chronic hepatitis C to seek help before these symptoms develop.

Many people may find it difficult to admit the need for help or the need to seek treatment if they do not have any physical symptoms.

Diagnosis and Assessment of Disease Severity

Because people who have hepatitis C often do not have symptoms, many of them learn they have liver disease after having routine blood tests. People who have elevated liver enzymes or antibodies to hepatitis C need further testing to determine whether they have an active hepatitis C infection, using the hepatitis C RNA polymerase chain reaction test to detect the amount of hepatitis C RNA in the blood. Further testing will help assess the extent of liver injury. The physician will perform an ultrasound of the liver and additional blood tests to rule out other possible causes of liver disease. The physician also will test the blood to assess whether the person needs to be vaccinated to protect against hepatitis A and B infection.

Liver Biopsy

After diagnosing hepatitis C in an individual, the physician needs to assess the severity of liver disease. The best way to definitively confirm liver disease is to take a sample of liver tissue in a liver biopsy. Examination of the liver biopsy sample (liver histology) by a pathologist will establish the severity of inflammation (the grade of disease) and level of scarring or fibrosis (the stage of disease). If the biopsy reveals moderate or severe inflammation, there is a high likelihood that the person may develop cirrhosis in the future. More importantly, the severity of fibrosis (stage) also predicts the progression to cirrhosis. A biopsy also establishes whether the person suffers from any other type of liver disease.

To obtain a liver tissue sample, the physician uses ultrasound or computed tomography (CT) to find the best spot to insert the needle, cleans the area with betadine, and anesthetizes the skin with lidocaine (see chapter 3, figure 3.1). Then, the physician inserts a needle between the ribs to remove a sample of tissue. Use of CT guidance has not been shown to offer any advantage over ultrasound guidance. Complications from the procedure are extremely rare (less than 1 in 2,000) but can include bleeding, perforation of an organ close to the liver (such as the colon, gallbladder, or lungs), pain, or infections. Because these complications are rare, most physicians consider the benefits of a liver biopsy to far outweigh the risks.

Alternatives to Liver Biopsy

Many people ask their physicians whether there are alternatives to liver biopsy for assessing fibrosis. At this time, other available methods are neither specific nor sensitive enough to detect the presence or gauge the severity of fibrosis. Many blood tests, such as FibroSURE, are commercially available, but they are not useful in identifying individuals who have intermediate fibrosis. Radiological techniques, such as FibroScan, are also being developed and need further validation in the United States. Currently, these tests are considered experimental and require further testing before they can replace liver biopsy. Most liver specialists consider liver biopsy the "gold standard" for assessing fibrosis. FibroScan (see chapter 3) may replace liver biopsy to assess progression of liver disease in the future. This technique is useful for ruling out cirrhosis, but it is not reliable for accurately diagnosing moderate severity of fibrosis.

From Inflammation to Fibrosis

Although inflammation is common in almost all people who have chronic hepatitis C, the presence of significant fibrosis, or scarring of the liver, indicates that the disease is progressing. In many people, this scarring will ultimately lead to cirrhosis. Fibrosis can be described in terms of mild (early), moderate (or intermediate), or severe (advanced), or established cirrhosis.

If a liver biopsy reveals fibrosis, the physician can assess the amount of fibrosis and number of septae (scar tissue extending from one portal tract to another) in a semi-quantitative fashion, using well-defined criteria. The Metavir scoring system uses four stages to describe the severity of fibrosis (table 6.1), and the Ishak system uses six stages (table 6.2). The Ishak (modified Knodell) scoring system is more descriptive than the Metavir system, using a wider scale (six stages rather than four). For example, F1 and F2 of the Metavir system correspond to F1, F2, F3, and F4 in the Ishak system.

Although most pathologists use either Metavir or Ishak staging to describe their findings, some pathologists use other ways to describe the severity of fibrosis. When discussing the results of their liver biopsy, individuals should ask their physician to clearly and thoroughly explain the findings so that they understand the severity of their liver disease.

Table 6.1. Metavir Scoring System for Fibrosis

Stage	*Symptoms*
Stage 0 (F0)	Normal, no fibrosis
Stage 1 (F1)	Fibrosis around portal tracts (portal fibrosis)
Stage 2 (F2)	Few fibrotic septae
Stage 3 (F3)	Numerous fibrotic septae
Stage 4 (F4)	Cirrhosis (extensive fibrosis with nodules)

Table 6.2. Ishak (modified Knodell) Scoring System for Fibrosis

Stage	*Symptoms*
Stage 0 (F0)	Normal, no fibrosis
Stage 1 (F1)	Fibrosis around *some* portal tracts
Stage 2 (F2)	Fibrosis around *most* portal tracts
Stage 3 (F3)	*Occasional* porto-portal bridging fibrosis
Stage 4 (F4)	*Marked* porto-portal and porto-central bridging
Stage 5 (F5)	Marked bridging with occasional nodules
Stage 6 (F6)	Cirrhosis

The author finds it easier to use the Metavir system to address the severity of fibrosis.

Is Fibrosis Reversible?

Until recently, many physicians believed that fibrosis is irreversible. However, some recent and emerging observations suggest that fibrosis can be reversed to some extent if the cause of fibrosis is eliminated. Studies of chronic hepatitis B have clearly demonstrated the possibility that early cirrhosis can be reversed after the hepatitis B virus is cleared. Many studies of people who have hepatitis C with fibrosis show that clearance of the hepatitis C virus reduces the severity of fibrosis. The current strategy to prevent or reverse the fibrosis in people who have hepatitis C infection is to eliminate the virus (achieving sustained viral clearance) with antiviral therapy. Many medications with the theoretical potential to prevent or reverse fibrosis either have been tested or are in various stages of development, but to date, no drug has been found to be effective in preventing fibrosis.

Despite the possibility that early cirrhosis is potentially reversible, no convincing evidence suggests that long-standing cirrhosis can be reversed.

From Fibrosis to Cirrhosis

In general, cirrhosis is the presence of a lot of fibrosis throughout the liver, with nodules. To the naked eye, a healthy liver normally has a smooth surface, but a liver that has cirrhosis has lumps and bumps.

Before cirrhosis develops, the liver has a lot of scar tissue extending from one portal tract to another portal tract or central vein in many areas of the liver. This stage of scarring is known as septate fibrosis, which, for all practical purposes, could be considered early cirrhosis. Moderate and severe fibrosis may indicate progressive and more aggressive liver disease.

Progression from Mild Disease to Cirrhosis

It is important to remember that for most people, the diagnosis of hepatitis C infection is just a warning, not a death sentence, as many perceive it. Approximately 20 to 30 percent of people who have hepatitis C will develop cirrhosis within 10 to 20 years after they become infected (figure 6.1). Approximately 30 percent may develop cirrhosis after 40 to 50 years. Given the length of time it may take for cirrhosis to develop in this group, a significant number of these individuals will die of causes other than the complications of hepatitis C infection. Also important to remember is that 30 to 40 percent of people who have hepatitis C may never develop any serious liver damage. This is an important consideration for individuals who have chronic hepatitis C and for their physicians before starting treatment. Not all people who have hepatitis C need immediate treatment, and people who have minimal liver damage could wait for better treatments to become available.

Many people who have a hepatitis C infection focus exclusively on hepatitis C while ignoring their general health (for example, controlling weight, managing diabetes, or managing high blood pressure). However,

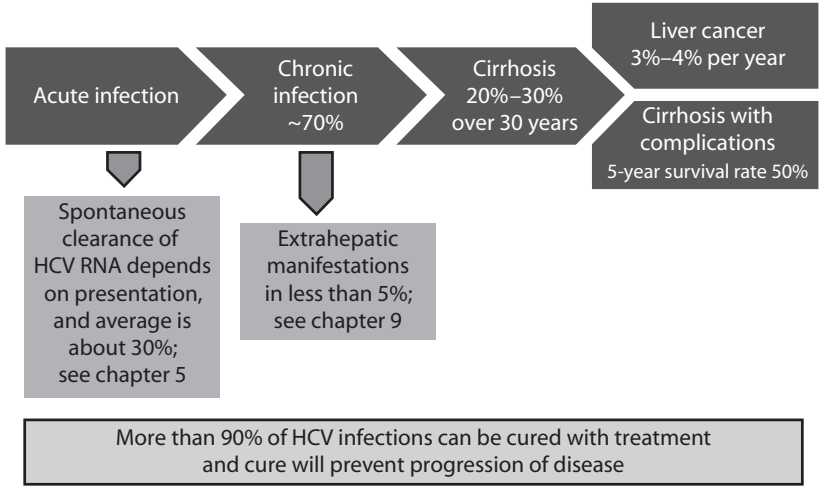

Acute infection
Chronic infection ~70%
Cirrhosis 20%–30% over 30 years
Liver cancer 3%–4% per year
Cirrhosis with complications
5-year survival rate 50%
Spontaneous clearance of HCV RNA depends on presentation, and average is about 30%; see chapter 5
Extrahepatic manifestations in less than 5%; see chapter 9
More than 90% of HCV infections can be cured with treatment and cure will prevent progression of disease

Figure 6.1. What could happen after infection by the hepatitis C virus (HCV) without curative treatment?

people who have hepatitis C can decrease their risk of preventable diseases by making changes in their lifestyle or following certain health-related guidelines.

Who Develops More Advanced Liver Disease?

Many studies have attempted to predict the progression of liver disease based on specific characteristics of the infected person and the virus. Although these studies show some trends, predicting disease progression for any individual is difficult without a liver biopsy or, in some cases, a series of biopsies. The most useful information, by far, in assessing the risk of progression to cirrhosis is the severity of fibrosis observed in a liver biopsy sample. Data show that the risk of cirrhosis is low if there is minimal or mild fibrosis on the initial biopsy. Among these individuals, 20 percent develop cirrhosis after 10 years. On the contrary, almost all people who have severe fibrosis develop cirrhosis within 5 years. People who have moderate fibrosis fall somewhere in between. In addition to fibrosis, individuals who have severe inflammation are more likely to develop progressive disease.

Individuals in certain groups or who have certain risk factors are at a greater risk of progressive liver disease (table 6.3). Although many of these factors can be useful in predicting disease progression in a group of people, they are not helpful when looking at a specific individual.

Alcohol is perhaps the most important risk factor that predicts progression to cirrhosis, and individuals who have hepatitis C should abstain from alcohol for several reasons, as discussed in the next section.

People with liver disease should abstain from alcohol completely.

Other risk factors for progression to cirrhosis include age and acquiring the hepatitis C infection through a blood transfusion. In some studies, individuals who acquired hepatitis C after the age of 50 were more likely to develop progressive disease and cirrhosis. Similarly, the risk of developing progressive disease was higher in individuals who developed hepatitis C infection through blood transfusion. Because older people are

Table 6.3. Factors That Predict Progressive Liver Disease

Severity of fibrosis, as seen on liver biopsy
Alcohol intake
Older age (over 50)
Severity of inflammation
Immunosuppression (in individuals who have received a transplant)
Co-infection with HIV or hepatitis B
Being male
Hepatitis C acquired through blood transfusion
Fat in the liver (steatosis)
Iron overload

more likely to receive blood transfusions, it is difficult to assess the risk from transfusion alone.

The presence of iron overload (high ferritin and high iron saturation) and fat in the liver (steatosis) may increase the risk of developing progressive disease and liver cancer. People who have too much iron in their blood may benefit from iron depletion. If a person does not have an obvious iron overload syndrome (hemochromatosis or secondary hemosiderosis), however, iron depletion is not helpful in delaying progressive liver disease.

> Iron supplements should be avoided unless the person has iron deficiency anemia.

Fat in the liver could be part of the hepatitis C disease process (especially with hepatitis C virus genotypes 1 or 3) or part of a metabolic syndrome (obesity, high cholesterol and triglycerides, and type 2 diabetes mellitus).

HIV infection makes hepatitis C–induced liver disease worse for many individuals, especially those who have low CD4 counts. For people who have acute hepatitis C, HIV infection decreases the likelihood of spontaneous clearance of the hepatitis C virus. For people who have chronic hepatitis C infection, HIV infection causes higher hepatitis C viral counts

and faster progression to liver disease. Chapter 10 provides more information about infection with both HIV and hepatitis C.

No convincing evidence suggests that the amount of hepatitis C virus in the blood (the viral load) and the virus's genetic subtype (genotype) predict the progression of disease. The only exception may be after organ transplantation, where high viral loads (more than 20 million IU) have been associated with rapidly progressive jaundice and fibrosis in a small number of people (a condition called fibrosing cholestatic hepatitis).

Although it is not proven, individuals who are obese, have hyperlipidemia, or have diabetes mellitus may benefit from reducing their weight and controlling their lipids and diabetes. More importantly, when individuals who have hepatitis C take measures to control some of these factors, it may improve their overall health and should become part of routine hepatitis C treatment and health maintenance.

The Effects of Alcohol

People who have a hepatitis C infection often ask their physicians whether they can drink alcohol and how much they can drink. Scientific studies show that people who have hepatitis C should not have any alcohol, because it adversely affects the hepatitis C virus clearance rate, progression to liver disease, and response to hepatitis C medication.

In general, approximately 10 to 20 percent of alcoholics without other risk factors (hepatitis C, hepatitis B, or metabolic syndrome) develop liver disease. However, people with alcoholism and hepatitis C have a much higher risk of developing cirrhosis. Although the precise reasons remain unknown, hepatitis C infection is more common among people with alcoholism. Approximately 10 to 15 percent of alcoholics have evidence of active hepatitis C or previous exposure to hepatitis C infection, possibly because both drug and alcohol use are common among individuals susceptible to these addictive substances.

Effect on Hepatitis C RNA Levels and Disease Progression

Alcoholism may prevent spontaneous viral clearance after hepatitis C infection, leading to chronic infection and liver disease. Experimental studies show that alcohol dramatically increases the replication of the hepatitis C virus and minimizes the effects of the antiviral medication interferon. Most studies show increased hepatitis C RNA levels in alcoholics compared with non-alcoholics. Even a moderate amount of alcohol (one or two drinks a day, or a total of seven drinks a week) has a significant impact on hepatitis C RNA levels and progression to cirrhosis. In one study, 50 percent of people who had hepatitis C and ingested alcohol developed cirrhosis, compared with only 10 percent of individuals who did not drink alcohol.

Overwhelming evidence suggests that even small amounts of alcohol may increase the progression of liver fibrosis and the development of cirrhosis. The severity of disease relates to the amount of alcohol and duration of drinking. One study reported that the lifetime consumption of alcohol might increase the risk for development of cirrhosis; in this study, people who developed cirrhosis drank five times as much as individuals who did not develop cirrhosis.

These studies clearly suggest that for the liver, hepatitis C and alcohol are a harmful combination. To prevent rapid disease progression and improve the treatment cure rate, the single most important thing that individuals who have hepatitis C should do is to completely abstain from alcohol. Table 6.4 summarizes the detrimental effects of alcohol consumption.

Many people ask their physicians: "Why do many of my friends drink heavily and not develop liver disease?" Although there is no clear answer,

Table 6.4. Effects of Alcohol on Hepatitis C

Alcohol increases hepatitis C virus replication.
Alcohol increases the risk of fibrosis and cirrhosis in people who have hepatitis C.
Consumption of alcohol during treatment reduces the treatment response rate.
Alcohol increases the risk of liver cancer.

Table 6.5. All Types of Alcohol Have the Same Effect on the Liver

Type of Alcoholic Drink	*Amount of Pure Alcohol (grams)*
One glass of wine (100 ml)	10–14
One can of beer (250 ml)	10–14
One glass of whiskey (30 ml)	10–14

it is important to recognize that certain individuals are genetically susceptible to developing alcohol-induced liver disease. For example, women are, in general, more susceptible than men, and Asians are more susceptible than Caucasians. Unfortunately, there are no easy ways or tests to identify genetically susceptible individuals, and genetic susceptibility may not apply to individuals who have hepatitis C infection.

There is also a myth that the type of alcohol consumed makes a difference in the development of liver disease. Many consider beer and wine less toxic than whiskey, brandy, or rum, but this supposition is false (table 6.5). The amount of alcohol—not the type of alcohol—is what matters in the progression of liver disease. The liver does not discriminate between beer and wine, or whether it is cheap or expensive liquor. One glass (100 ml) of wine, one can (250 ml) of beer, and 30 ml of whiskey contain the same amount of pure alcohol (10 grams). The quantity of alcohol consumed and the duration of the use of alcohol determine the severity of liver damage, and for people who have hepatitis C infection, alcohol greatly increases the risk of severe liver damage. It also increases the risk for the development of liver cancer.

Alcohol in excess (more than three drinks a day for men and more than two for women) is damaging even to healthy people (table 6.6). However, for individuals who have liver disease or current (or previous) hepatitis C infection, the combination of hepatitis C and alcohol is lethal.

Effect on Treatment Response

Many studies show that the cure rate (the sustained hepatitis C RNA clearance) is lower among alcoholics than non-alcoholics. Among people who drink heavily, the response rates are indeed low. If an individual who

Table 6.6. How Much Alcohol Is Safe?

Group of Individuals	*Safe Amount*
Healthy men	Maximum: 3 drinks (30 grams of alcohol) per day
Healthy women	Maximum: 2 drinks (20 grams) per day
People who have hepatitis C People who have other liver diseases People who have received a liver transplant	*None*

has hepatitis C is not prepared to immediately and completely abstain from alcohol, the physician may delay treatment. Increasing evidence suggests that even small amounts of alcohol may affect the person's treatment response.

Some strategies for preventing the progression of hepatitis C:

- Avoid alcohol completely.
- Receive vaccination for hepatitis A and hepatitis B. (People with hepatitis C are likely to develop liver failure if they become infected with hepatitis A or B.)
- Maintain good general health, weight, and lifestyle.
- Control cholesterol and triglycerides, hypertension, and diabetes.
- Stop smoking.
- Seek treatment for hepatitis C infection. A cure will reduce the risk of progression to cirrhosis and reduce the risk of developing liver cancer.

Individuals who have cirrhosis should see a liver specialist and should be screened regularly for liver cancer (see chapter 12) and for complications of cirrhosis (such as esophageal or gastric bleeding).

7

Hepatitis C in Children

Many aspects of hepatitis C are different in children than in adults, including the method of transmission, the natural history, and complications, and only a small proportion of people with chronic hepatitis C are children. A lot of progress has been made in treating children who have hepatitis C, and most children can be cured and live a normal life. Despite these advancements, additional research in both disease prevention and treatment needs to be done to help address hepatitis C infections in children.

Approximately 240,000 children in the United States have hepatitis C antibodies, but only 68,000 to fewer than 100,000 are infected with the virus (as confirmed by positive results on the hepatitis C RNA polymerase chain reaction test). The prevalence of hepatitis C infection in children in the United States is low, ranging from about 0.05 to 0.36 percent (table 7.1), as it is in other developed countries. However, in developing countries, the prevalence ranges from 1.8 to 5.8 percent, and in some countries, such as Cameroon, the rate of childhood hepatitis C is as high as 14.5 percent. Higher prevalence rates are also observed in Egypt, sub-Saharan Africa, the Amazon basin, and Mongolia.

The advent of blood screening for hepatitis C in 1990 had a significant impact on the rate of infection in children, as it did for the general population. Children who had hemophilia and received multiple transfusions of blood or blood products before 1990 had infection rates ranging between 50 and 95 percent. Among children who received multiple

Table 7.1. Prevalence of Hepatitis C in Children in the United States, 2014

Group of Children	*Prevalence*
Younger than 12 years old	2 per 1,000 (0.2%)
12 to 19 years old	4 per 1,000 (0.4%)
Children who have hemophilia	50% to 95% (if they received blood transfusions before 1990)
Children who have cancer other than liver cancer	10% to 20% (if they received blood transfusions before 1990)

blood transfusions before 1990, for cancers or during surgery for congenital heart disease, 10 to 20 percent were infected with hepatitis C. Children who received hemodialysis treatment before 1990 also had a 10 to 20 percent hepatitis C infection rate.

Methods of Transmission

Hepatitis C can be transmitted only through blood or blood-containing body fluids. Because of the improved blood donor screening practices, blood transfusion is now rarely associated with hepatitis C infection.

Transmission from mother to child during pregnancy or delivery, although rare, currently remains the main method by which children become infected with hepatitis C. About 1 percent (range, 0.1 to 2.4 percent) of pregnant women are infected with hepatitis C, and only 4 to 7 percent of women who have an active hepatitis C infection transmit it to their children. The transmission rates are higher when mothers are also infected with HIV and have viral loads higher than 1 million copies per milliliter.

The effect of other factors—including severe liver disease in the mother, amniocentesis, type of delivery, and complications of delivery—on mother-to-child transmission remains largely unknown. There are no specific recommendations on the method (cesarean versus vaginal) or timing of delivery to prevent transmission of hepatitis C infection. Also, breastfeeding does not increase the risk of transmission unless the mother's nipples are bleeding.

The risk to children living in households with individuals who have hepatitis C is believed to be low, although this is not proven. The prevalence of hepatitis C infection among nonsexual household contacts of infected individuals ranges from 0 to 6.5 percent. The higher rate among family members in some studies may result from other methods of transmission. In a household where a person is infected with hepatitis C, it is important to take extreme care to prevent children or other family members from sharing razors or toothbrushes.

A few studies have examined whether hepatitis C can be spread from child to child and found this risk to be extremely low. Based on these findings, the American Academy of Pediatrics recommends that children who have hepatitis C do not need to have any restrictions on school attendance, day care attendance, and participation in sports, including sports with body contact.

In low-income countries, a significant number of children get infected through unsafe blood products and contaminated needles (reused), syringes (reused), and medical instruments. Unfortunately, this source of transmission will remain a major route of infection in low-income countries.

Symptoms

As noted in chapter 5, people who have acute hepatitis C infection may not know they are infected because they do not have any symptoms, and this holds true for children. To date, no cases of acute liver failure have been reported in children.

Most children who have chronic hepatitis C do not manifest any physical or cognitive symptoms until they develop advanced liver disease. Autoimmune manifestations (that is, the immune system damaging organs other than the liver) of hepatitis C infections are also rare in children. Diseases associated with hepatitis C such as cryoglobulinemia (high level of a protein that causes organ injury), vasculitis (inflammation of blood vessels), and porphyria (a group of diseases caused by abnormalities in the chemical steps that lead to production of heme, an essential component of blood proteins) have not been reported in children.

Testing

The rate of hepatitis C infection in children may be underestimated, because children often have no symptoms and liver tests are rarely done in children. Children born to mothers who have hepatitis C infection should be routinely checked for hepatitis C. Routine hepatitis C screening of children is not needed if the child has no other risk factors, such as an infected mother. In developed countries, children are tested only when they have one or more risk factors, such as transfusion of blood products or a mother who has the infection. However, it is advisable to routinely test for hepatitis C infection in children who are born in countries with a higher prevalence of hepatitis C.

Natural Progression of the Disease

The natural progression of a hepatitis C infection in children depends on how the child got the infection. In children who became infected through blood transfusion, the underlying disease, such as hemophilia or cancer, may predict how hepatitis C progresses. For example, for children who have thalassemia, iron overload in the blood may cause liver disease (including cirrhosis), and when they become infected with hepatitis C, their disease progression may be faster.

The risk of serious injury to the liver appears to be lower for children who have hepatitis C than for adults. In one study, 8.5 percent of individuals who acquired hepatitis C as children, possibly through blood transfusion during the treatment of childhood cancer, developed cirrhosis 9 to 27 years after their cancer treatment. Although cirrhosis can occur in children, it occurs with less frequency than in adults. In fact, the pediatric liver transplantation registry shows that hepatitis C infection was the reason for liver transplantation in only 9 of 941 children who received liver transplants between 1995 and 2001.

The natural history of hepatitis C acquired from mothers remains poorly defined. Infection occurs when the child's immune system is not completely developed. For a short amount of time, some infants may have

the virus in their blood without hepatitis C infection. Other infants may have an acute, self-limiting infection that is noticeable. Children who acquire hepatitis C from their mother have a rate of spontaneous clearance as high as 50 percent. As in adults, certain genetic characteristics may also determine the spontaneous cure rates (for example, a genetic marker known as IL28B appears to influence both spontaneous and treatment-related cure in the infected child). For children with hepatitis C, unlike adults, the rate of progression to chronic hepatitis C infection is low. Further studies are required to characterize the disease pattern in hepatitis C infection acquired from the mother.

Children who develop chronic hepatitis C infection show fluctuating levels of viral counts and normal or near normal alanine aminotransferase levels. However, liver biopsies in almost all children who have chronic hepatitis C infection show evidence of chronic hepatitis. In the first one to two decades, the disease activity in the liver seems to be mild, and most children develop only minimal fibrosis.

Treatment

For parents and physicians, making the decision to treat a child with interferon is a challenging one. Although interferon-based treatment is the standard therapy in adults, it should not be used for children younger than 3 years old, because of the medication's effects on the nervous system and children's growth and development. Although early studies used mostly standard interferon (given through injections three times a week) and daily ribavirin, more recent studies have used pegylated interferon (given through injections once a week) in combination with daily ribavirin for 24 to 48 weeks.

The treatment response rates in children with interferon alone (called monotherapy) are higher than in adults. An analysis of data from many studies showed a virus clearance response in 35 percent of 270 children being treated with interferon. The higher cure rate in children than in adults may be related to a number of factors, including the early stage of the disease in children, the treatment dose having a higher amount of

interferon compared with body weight in children, and the absence of harmful practices such as alcohol use.

Many studies have shown that the use of standard interferon in combination with ribavirin has a higher treatment response rate than interferon alone. Between 40 and 50 percent of children who had hepatitis C, genotype 1, infections were cured, and most children did not have serious side effects to ribavirin. As occurs in adults, children experienced a breakdown of red blood cells (hemolytic anemia), depending on the dose of ribavirin; when the dose was decreased this effect was reduced, so treatment rarely had to be stopped. Because many children develop antibodies to themselves with long-term interferon treatment, doctors should carefully monitor whether a child develops this type of immunity.

More recently, children have been treated with pegylated interferon (once a week) in combination with ribavirin. These studies show better cure rates than the standard interferon-ribavirin combination. The response rates, as in adults, depend on the genotype of the virus. A systematic review of treatment in children showed up to 50 to 70 percent cure rates with genotype 1, and 80 to 100 percent cure rates with other genotypes (2, 3, or 4). Based on these data, pegylated interferon in combination with ribavirin will become the standard of care for children older than 3 years. The duration of treatment depends on the genotype (24 weeks for genotypes 2 and 3; 48 weeks for other genotypes).

The Food and Drug Administration has approved pegylated interferon alfa-2b (manufactured by Merck) in combination with ribavirin for children older than 3 years. No other treatment has been approved by the FDA for children who have hepatitis C.

With the rapid progress we have made in the treatment of hepatitis C in adults, in the near future we may see more effective, interferon-free treatment with minimal side effects for children who have hepatitis C. The newly approved drug sofosbuvir (Sovaldi; an effective inhibitor of the viral protein NS5B in adults, when used in combination with either ribavirin or interferon and ribavirin) is not approved for use in children. Similarly, Harvoni (a combination of sofosbuvir and ledipasvir) is not approved for use in children.

Prevention

Preventing hepatitis C infections in adolescents requires educating them about high-risk behaviors, such as alcohol use and injection drug use.

More research is needed on reducing the risk of transmission of infection from other children. Providing treatment after exposure during pregnancy or delivery is not recommended for infants born to hepatitis C–infected women. Mothers who also have HIV should be treated aggressively with antiretroviral therapy. In addition, some studies recommend that physicians avoid the use of internal fetal scalp monitors or breaking the mother's water too early (more than six hours) before delivery.

Currently, testing of all pregnant women for hepatitis C is not recommended, but it may be prudent to screen women who have HIV, a history of injection drug use, sexual partners who are injection drug users, a history of blood transfusion before 1992, or who live in areas of high infection rates. Although routine screening of pregnant women is not recommended, the U.S. Preventive Services Task Force recommends routine screening of children born to mothers who have hepatitis C.

- Hepatitis C infection in children is rare in high-income countries.
- Mother-to-child transmission is the most common way that children become infected with hepatitis C in developed countries. Further research is needed to identify factors that affect transmission during pregnancy and delivery and to help develop effective ways to prevent transmission.
- It is important to identify infected children by screening children born to mothers who have hepatitis C.
- Children who have hepatitis C should be monitored by a pediatric liver specialist to check the progression of liver disease.
- The progression of liver disease is slow in children, but to reduce the risk of cirrhosis and liver cancer, physicians should try to clear the virus.
- The only approved treatment for hepatitis C in children is pegylated interferon alfa-2b in combination with ribavirin. No treatment is

approved for children younger than 3 years old. The cure rate with pegylated interferon and ribavirin is between 50 and 100 percent, depending on the genotype, but it is associated with side effects.

- Recent progress in finding treatments suggests that in the near future, when interferon-free, direct-acting antiviral medications are approved for use in children, almost all children may be cured, with minimal side effects.

8

Cirrhosis, Advanced Liver Disease, and Liver Cancer

For nearly 70 percent of people infected with hepatitis C, acute infection leads to chronic infection. Chronic hepatitis C is a serious disease that can result in long-term health problems, such as cirrhosis and liver cancer. Approximately 20 to 30 percent of people who have chronic hepatitis C will develop cirrhosis within 10 to 20 years after acquiring the infection. An additional 30 percent may go on to develop cirrhosis 40 to 50 years after becoming infected. However, not all people who have chronic hepatitis C will develop cirrhosis; approximately 30 to 40 percent of individuals will never develop any serious liver damage. During this time period, people who have hepatitis C have the opportunity to maintain the kind of lifestyle choices that will benefit their overall health.

Cirrhosis is a serious development of hepatitis C infection, as are the complications that result from it. In chapter 1, we outlined the liver's essential functions, which include making proteins, helping the body fight infections, cleansing the blood, helping to digest food, and storing energy. If chronic hepatitis C progresses to cirrhosis, the liver cannot perform these jobs effectively.

In this chapter, we look at the signs, symptoms, and complications of cirrhosis, including liver cancer, also known as hepatocellular carcinoma or hepatoma.

Table 8.1. Symptoms and Signs of Advanced Liver Disease

Symptoms	*Signs*
Severe fatigue	Spider-like collections of blood vessels (spider nevi) on face, arms, or chest
Short-term memory problems	Loss of armpit or pubic hair in men
Jaundice	Testicular atrophy
Impotence in men	Prominent veins on the abdomen
Enlarged breasts in men (gynecomastia)	Fluid in the abdomen (ascites)
Abdominal or leg swelling (edema)	Flapping tremors (asterixis)
Vomiting blood or passing black stool	Wasting of muscles
Redness (erythema) of palms	

Signs and Symptoms

As mentioned in chapter 4, most people who have hepatitis C infection have no symptoms. If people do have symptoms, such as severe fatigue or jaundice, it usually means that the liver disease may have progressed to cirrhosis, and they should immediately consult a physician. Table 8.1 summarizes symptoms and findings on physical examination. Because these symptoms and signs could also result from conditions other than liver disease, people should consult a physician before making any assumptions.

Major Complications of Cirrhosis

Cirrhosis, or scarring of the liver, can occur after many years as a result of liver disease or injury. If the cirrhosis is diagnosed early and its cause is treated, further damage may be halted or even reversed in some people. However, as cirrhosis progresses and more scar tissue forms, the liver cannot carry out its normal functions. Advanced cirrhosis is a serious condition. The complications of cirrhosis include the following:

- Fluid accumulation:
  - Distension of the abdomen with fluid (ascites)
  - Swelling of the legs (edema)
  - Swelling throughout the body (anasarca)
- Major gastrointestinal bleeding:
  - From enlarged veins of the esophagus (esophageal varices)
  - From large veins of the stomach (gastric varices)
  - From large veins of the colon or small intestine (ectopic varices)
- Bacterial infections:
  - Infection of the fluid that builds up in the abdomen (spontaneous bacterial peritonitis)
  - Urinary tract infection
  - Respiratory tract infection
- Change in mental status (hepatic encephalopathy):
  - Sleep pattern changes
  - Short-term memory problems
  - Confusion
  - Coma (rare)
- Liver cancer (hepatocellular cancer, or hepatoma)
- Muscle wasting

These major complications of cirrhosis are common and serious conditions. To better understand their causes and how to manage them, it is important to understand portal hypertension, an increase in the pressure within the portal vein caused by a blockage or resistance to blood flow through the liver. Most complications of cirrhosis, including fluid in the abdomen (ascites), variceal bleeding, and hepatic encephalopathy, are caused predominantly by portal hypertension.

Portal Hypertension

The portal vein, which carries blood from the intestine, pancreas, and spleen to the liver, supplies approximately 70 percent of the blood to the liver (see chapter 1, figure 1.4). The portal blood brings important nutrients from the intestine to be processed in the liver and allows the liver

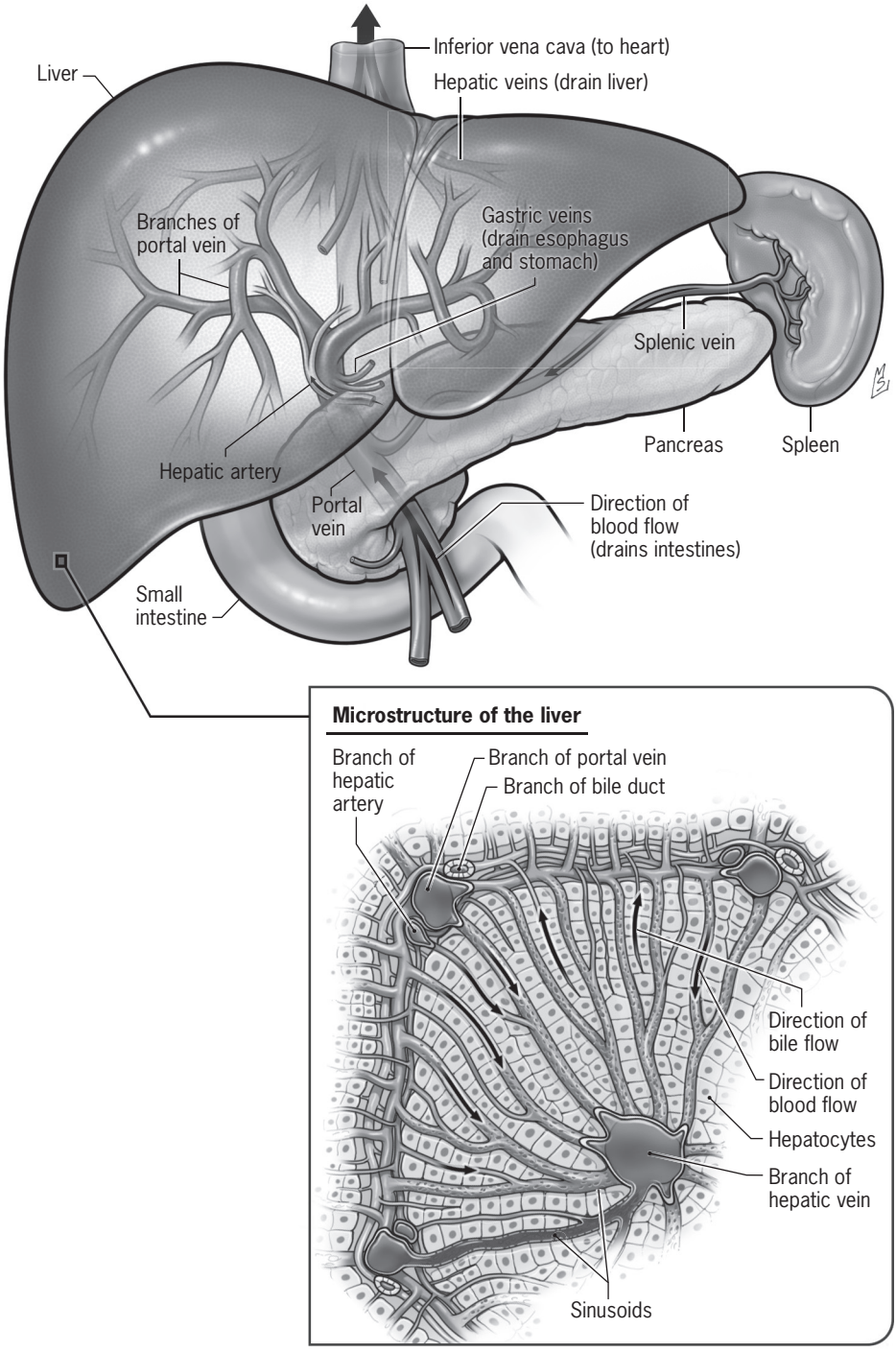


Figure 8.1. Liver anatomy, showing the relationship between blood vessels, liver cells (hepatocytes), and bile

to clear some of the toxins absorbed from the intestine. Most drugs are also processed in the liver after absorption from the intestine.

The remaining 30 percent of blood to the liver comes from the hepatic artery. The liver is unique because of this dual blood supply, which provides an advantage if the portal blood flow is blocked (by a blood clot, tumor, or scarring due to cirrhosis) because the hepatic artery can compensate, to some extent, by increasing the blood flow to the liver. However, if the hepatic artery is blocked, the portal vein cannot increase the blood flow to the liver.

Under healthy conditions, the liver can accommodate large increases in blood flow without increasing the pressure in the portal vein. After eating, for example, blood flow to the liver from the portal vein and its smaller veins increases. The blood flows through small channels called sinusoids, bathing the liver cells (hepatocytes), then drains into small veins (branches of hepatic veins) (figure 8.1). These small veins join to become three relatively large hepatic veins (the right, middle, and left hepatic veins). Blood in the hepatic veins drains into the inferior vena cava, the large vein that empties the blood from the lower part of the body into the right side of the heart.

Normal pressure in the portal vein is less than 5 to 12 mm Hg (millimeters of mercury), and the pressure difference between the portal vein and the inferior vena cava (the porto-venous gradient) is less than 5 mm Hg. In a healthy individual, this pressure difference remains more or less constant, and in a healthy liver, large increases in blood flow can be easily accommodated without an increase in portal pressure.

For people who have cirrhosis, the blood flow has greater resistance because of scar tissue, nodules, and blood clots in the small branches of the portal vein. In addition, people with cirrhosis experience changes in their nervous system and hormones that also increase resistance to blood flow in the liver. Combined, these factors lead to an increase in pressure in the portal vein, which is called portal hypertension (figure 8.2).

Although other factors can cause portal hypertension, cirrhosis is the most common cause. Portal hypertension is diagnosed when the porto-venous gradient exceeds 5 mm Hg, but the complications of portal hypertension usually appear when pressure exceeds 10 mm Hg. There are no reliable



Figure 8.2. Cirrhosis of the liver can lead to portal hypertension

noninvasive ways to measure portal pressure. Direct measurement could be made by inserting a needle into the liver and advancing the needle into the portal vein, but it is rarely done in this way. Usually, the pressure is measured indirectly by advancing a catheter, with a balloon at the catheter tip, into the hepatic vein (the catheter is inserted into a neck vein and then advanced), then taking pressure readings with the balloon inflated (hepatic vein wedge pressure) and deflated (hepatic vein free pressure). The difference between wedge pressure and free pressure (the hepatic vein wedge pressure gradient) is an approximation of the portal pressure gradient.

What Causes Portal Hypertension in Cirrhosis?

The development of portal hypertension in cirrhosis is complex. The scarring and nodules that occur with cirrhosis cause perhaps an estimated 60 percent of the resistance to blood flow through the liver (through small portal veins and sinusoids). Some nervous system and hormonal changes can also increase resistance to blood flow. Approximately 40 percent of resistance to blood flow in cirrhosis may be caused by these potentially reversible dynamic changes in the liver.

In addition to increased resistance to blood flow in cirrhosis, the amount of blood flowing to the liver from the portal vein increases, caused by the widening of the blood vessels inside the abdomen (the splanchnic arteries). This tremendous increase in blood flow and increased resistance in the liver leads to a greater increase in portal pressure. The blood circulating through the body cannot decrease the

pressure as it continues to increase, and when the porto-venous pressure gradient reaches 10 to 12 mm Hg, complications appear.

Fluid in the Abdomen (Ascites)

A major complication of cirrhosis is fluid buildup in the abdomen (ascites), which can be accompanied by swelling of the legs (edema). Initially, people who have ascites may not have discomfort, other than from the cosmetic appearance caused by a large accumulation of fluid. However, as ascites progresses, people may feel significant discomfort and pain and may have difficulty breathing.

To help control the buildup of fluid in the abdomen, a physician will probably recommend a sodium-restricted diet. Usually, individuals who have ascites must not have more than 2,000 mg of sodium per day and need to learn the sodium content in their food and adjust their diets accordingly. Because most processed foods are high in sodium, restricting processed foods and maintaining a healthy diet is highly recommended. It may be helpful to seek the help of a nutritionist or registered dietician to help make dietary changes.

If sodium restriction is not effective in managing ascites, the physician will prescribe medications (called diuretics) that help the body produce more urine, such as furosemide and spironolactone. Furosemide is fast-acting and may cause a loss of potassium; spironolactone acts by a different mechanism and conserves potassium. Taking a combination of the two medications helps keep potassium levels steady and avoids the need for potassium supplements.

For the person who has ascites, the physician will first prescribe a small dose of spironolactone with or without furosemide and, depending on the response, will then adjust the dose accordingly. Because higher doses may cause complications and kidney failure, individuals should carefully follow the physician's dosage instructions, and it is extremely important to follow a sodium-restricted diet.

To reduce the amount of fluid, a physician may periodically insert a needle through the abdominal wall and remove five to eight liters of fluid (a process called paracentesis). The physician decides where to place the

needle based on ultrasound examination. When removing a large amount of fluid, the physician also gives the patient albumin to prevent reduced kidney circulation and complications such as kidney failure.

> Please ask your physician whether you should get albumin infusion when fluid is removed to relieve abdominal discomfort. Although it is the standard of care, it could be overlooked. Albumin infusion is given to avoid kidney dysfunction.

In advanced stages of liver disease, even diuretics are not effective in controlling ascites. For people who have advanced liver disease, a liver transplant may be their best treatment option. Transjugular intrahepatic portosystemic shunt (TIPS) surgery may be successfully used for some people, but the procedure may result in confusion (encephalopathy) and, in a significant minority, may be fatal.

Spontaneous Bacterial Peritonitis

People who have ascites can experience a serious complication called spontaneous bacterial peritonitis, a bacterial infection that develops in the fluid. This complication can cause death in close to 30 percent of people who have ascites. For that reason, anyone with ascites who experiences fever, a change in mental status, or abdominal pain must consult a physician immediately. To diagnose this condition, the physician will examine the ascitic fluid to calculate the number of white cells; this is done by inserting a needle into the abdomen and removing a sample of the fluid. For most people, antibiotics and intravenous albumin can cure the infection if it is diagnosed early. People who develop this infection once are more likely to develop repeated infections, so to prevent recurring infections, the physician may prescribe life-long antibiotics.

Variceal Bleeding

As pressure builds up in the portal vessels, the body's first line of defense is to open up new blood vessels, or collaterals, to bypass the liver. When

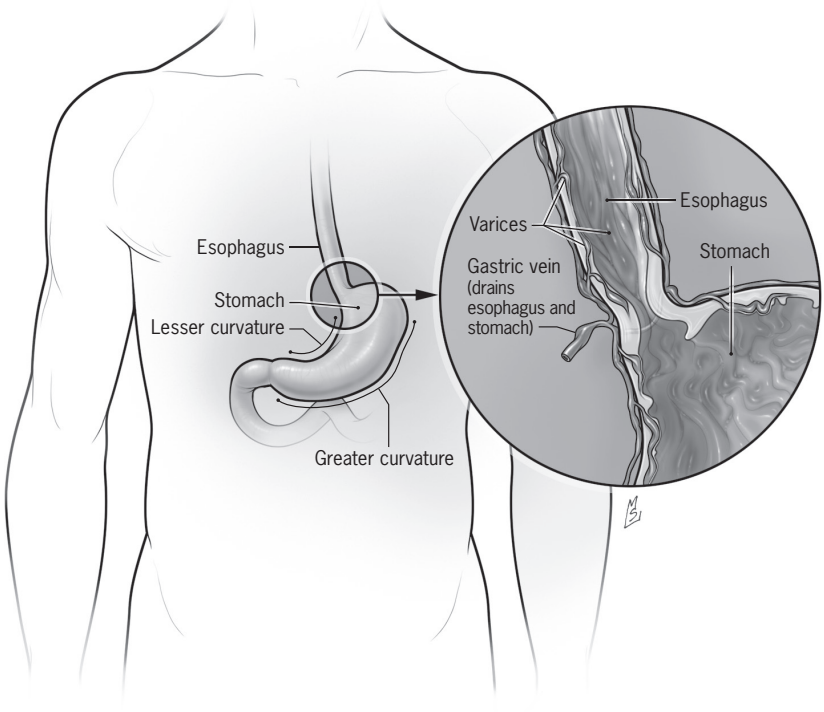


Figure 8.3. Esophageal varices as seen from inside the esophagus (shown in longitudinal section)

these blood vessels dilate to accommodate the increased blood flow they are called varices, and they may rupture, causing catastrophic bleeding. Varices in the stomach or esophagus are a serious and unpredictable complication of cirrhosis (figure 8.3). Each time a blood vessel ruptures, there is a 20 to 40 percent risk of death. Approximately one-third of all deaths in people who have cirrhosis can be directly attributed to bleeding of varices.

The risk of death after bleeding of varices and the long-term survival after the first bleeding episode are directly related to the severity of liver disease.

Prevention of the First Bleeding

A physician can assess a person's risk of bleeding by looking into the esophagus and stomach, using a flexible tube with a light and video

camera, a procedure called an endoscopy. Based on the size of the veins, their color, and other characteristics, the physician can predict the risk of bleeding.

If the risk is high, the physician may recommend medications (either propranolol or nadolol) to reduce the risk. These drugs do not eliminate the risk completely, but they reduce the risk by approximately 60 percent. The physician is likely to start with a small dose, and then will slowly increase the dose to get to a heart rate between 50 and 60 beats per minute. People at risk for bleeding from varices in the esophagus must remain on these medications for the rest of their lives (or until they have a liver transplant).

Another option for reducing the risk of bleeding is a procedure called variceal banding. During this procedure, a physician inserts an endoscope into the esophagus and stomach, sucks the large blood vessel into a cap attached to the end of the endoscope, and puts rubber bands over the blood vessel to stop the blood flow to that vein. Banding is a relatively simple outpatient procedure that has few, rare risks, including bleeding and stricture (narrowing of the esophagus). This procedure may need to be repeated two to four times over a period of three months before the veins disappear (are thrombosed).

The physician may suggest both medication and banding options to individuals with varices, or may prefer to recommend just one treatment, based on other factors. Banding is also offered if a person cannot tolerate the medications because of asthma or severe fatigue.

Sudden (Acute) Bleeding Episodes

It is not uncommon for a person to be diagnosed with cirrhosis for the first time after major bleeding from the stomach or esophagus. Individuals who have cirrhosis and have any signs of bleeding, such as vomiting blood, blood in the stool (red or black stool), or significant dizziness, should immediately go to the hospital and tell a physician that they have cirrhosis. Early intervention can greatly improve their chances of recovery.

The physician in the emergency room will start immediate resuscitation, which includes assessing and replacing the blood lost, protecting

the person's airway, administering intravenous antibiotics to prevent infection, and correcting clotting abnormalities (transfusing platelets, if they are very low, or fresh frozen plasma). The physician may also prescribe medications such as somatostatin or octreotide (drugs that reduce the pressure inside the varices) to stop the bleeding.

When the person is adequately resuscitated and stabilized, the physician will perform an endoscopy to make the diagnosis and stop the bleeding (by banding or by injecting chemicals into the bleeding veins). If the bleeding continues despite a combination of medicines and banding, or when banding is not possible because of massive bleeding, the physician may compress the bleeding vessels with a balloon (a process called balloon tamponade). Most bleeding will be stopped by these means. If all of these methods fail, the physician may decide to do a TIPS procedure. This involves making a shunt between the portal vein and hepatic vein by placing a coil in the liver, using a catheter, to reduce the pressure in the portal vein. TIPS is usually done by an experienced interventional radiologist, using a catheter introduced into the liver through one of the neck veins.

How to Prevent Bleeding Again

After one episode of bleeding, a person's risk of bleeding again is high. Among people who survive the first bleeding episode, 50 to 80 percent may have varices rupture again within two years, and most people have another bleeding episode within six weeks of the first. Just as with preventing a first bleeding episode, the options to prevent repeated bleeding of varices include banding or medications (propranolol or nadolol). Most physicians use a combination of medications and banding to prevent rebleeding, because some studies show that this is superior to either treatment alone.

When medications and banding are not successful in preventing repeated bleeding episodes, a physician may recommend alternative procedures. Most physicians opt to do a TIPS procedure in these situations. TIPS is effective in preventing repeat bleeding episodes, but it has a high risk of the shunt becoming narrow or blocked. For the best results, the physician has to periodically check and change the shunt to

ensure there is no blockage, but this monitoring is expensive. Shunt surgery in which the portal vein blood flow is redirected to bypass the liver is reserved for people who have mild liver disease; it is rarely performed these days because the same results can be achieved by the minimally invasive TIPS procedure. Shunt occlusion is less common after shunt surgery, but the likelihood of immediate complications is higher.

For people who have advanced liver disease, the above treatment options are not likely to improve their liver function or their survival. For these patients, liver transplantation, which has a five-year survival rate of up to 80 to 90 percent, is the best treatment option.

Varices in the Stomach (Gastric Varices)

Among people who have cirrhosis, 6 to 16 percent develop swollen blood vessels, or varices, in the stomach, usually with varices in the esophagus. In rare cases, a person may have only stomach varices, such as occurs with blood clots that develop in the vein in the spleen (a condition called splenic vein thrombosis). The risk of death from stomach varices bleeding (first or repeat bleeding) is more than 50 percent (higher than for esophageal varices bleeding).

When patients have sudden bleeding from stomach varices, a physician will try to control the bleeding by placing an inflated balloon (balloon tamponade) in the stomach. If the bleeding is in the upper part of the stomach (fundus) and a balloon tamponade does not stop the bleeding, a physician will perform a TIPS procedure. The physician will perform banding of stomach varices only if the bleeding is in the lesser curve of the stomach (see figure 8.3) or if the patient has bleeding within a hernia in the stomach. The physician could also inject glue (cyanoacrylate) into the varices in the upper part of the stomach (fundus) during active bleeding or, preferably, after the initial bleeding has stopped. This procedure is an effective treatment, although the Food and Drug Administration has not approved the use of glue for this purpose. In other countries, variceal glue injection is the preferred first option for the treatment of gastric varices.

Varices in Other Organs

In a small number of people who have cirrhosis (between 1.6 and 5 percent), bleeding may occur in organs other than the stomach or esophagus. The most common organs with varices that usually co-occur with esophageal varices include the small and large intestines and the rectum. Rarely, these varices may be caused by blood clots, tumors, or birth defects. Regardless of the cause, the method used to treat these episodes of bleeding depends on the physician's expertise, the location of bleeding, and the severity of the person's liver disease. A physician may decide that shunt surgery or TIPS is best for treating bleeding in certain areas of the small and large intestines.

Hepatic Encephalopathy

As cirrhosis and liver disease progress, people may develop memory problems and, later, may develop confusion. These symptoms, known as hepatic encephalopathy, are caused by toxins not eliminated from the body by the liver.

A healthy liver processes ammonia and other toxins from the intestine. When a person has cirrhosis, this process may not take place, because their liver is not working properly and blood is being diverted through other veins and bypasses the liver. When this happens, these toxins may reach the brain, causing a variety of symptoms including sleep disturbances, memory problems, confusion, and, in extreme cases, coma.

These symptoms are often brought on by constipation from a high-protein diet. Although eating a normal amount of protein is encouraged, people who have advanced cirrhosis should avoid high-protein diets and should make every effort to increase their fiber intake, which may help them avoid constipation. People who have advanced cirrhosis are encouraged to eat a diet high in vegetables. Also, physicians may prescribe a medicine called lactulose, a syrup that causes an increase in bowel movements and changes the pH and bowel microorganisms, thereby reducing the amount of ammonia formed and absorbed.

If lactulose does not work in relieving encephalopathy, the physician may prescribe antibiotics, such as rifaximin (Xifaxan), metronidazole, or neomycin. Rifaxamin, a nonabsorbable antibiotic, is preferred because of its efficacy and relatively better side effect profile. The only disadvantage is a higher cost than other antibiotics. When none of these approaches are successful, the physician may recommend a protein-restricted diet.

Often, encephalopathy is brought on by bleeding, infection, electrolyte abnormalities, or kidney failure.

Liver Cancer and Other Complications

Other complications of cirrhosis include liver cancer (hepatocelluar carcinoma), osteoporosis, and, in advanced cases, vitamin and mineral deficiencies. Malnutrition is also common in patients who have advanced cirrhosis.

Liver cancer (hepatocellular carcinoma or hepatoma) is one of the most dreaded complications of cirrhosis and is often diagnosed late, when treatment options are limited. Liver cancer is one of the most common cancers. Worldwide, liver cancer causes more than 1.3 million deaths per year, which is approximately 10 percent of all adult deaths. The main causes of liver cancer are hepatitis B and hepatitis C. Liver cancer and its causes, signs and symptoms, diagnosis, and treatments are discussed in chapter 12.

> People with cirrhosis should undergo screening for liver cancer every six months. Early liver cancer can be treated very effectively.

9

Impact of Hepatitis C on Organs Other than the Liver

Hepatitis C infection may affect other organs besides the liver. People who suffer from or suspect that they may have any of the conditions described in this chapter should consult with their physician on whether the condition could be caused by hepatitis C. Individuals who may not be experts in hepatitis C infection, including physicians and other caregivers, may be unaware of such an association, but notifying them about symptoms may alert them to a possible association and lead to better management of the disease.

What Conditions Other than Liver Disease Are Associated with Hepatitis C?

Approximately 5 percent of people who have hepatitis C may develop diseases in organs other than the liver (known as extrahepatic manifestations of hepatitis C infection). Many physicians consider hepatitis C to be a generalized disease, and almost all people who have the disease have mild symptoms involving organs other than the liver. However, only a small number of these people have symptoms severe enough to suggest that they are caused by hepatitis C.

The conditions that affect other organs are believed to be caused by activation of the immune system resulting from chronic hepatitis C infection and are not caused directly by the hepatitis C virus. The precise mechanisms for this immune system activation remain unknown. The

immune system is activated by the increase in white blood cells (also called lymphocytes) that regulate the immune system. Two types of white blood cells respond to the hepatitis C virus—B lymphocytes and T lymphocytes, also called B cells and T cells—and these cells are, in turn, responsible for a variety of conditions in other organs, particularly the skin and kidneys.

The conditions that affect other organs can be divided into several groups based on the strength of the scientific evidence that supports the association with chronic hepatitis C infection (table 9.1). It is

Table 9.1. Conditions Possibly Associated with Hepatitis C Infection

Strong association (a significant amount of evidence to indicate a relationship between the condition and hepatitis C):
Mixed cryoglobulinemia and vasculitis (thickening of blood proteins and inflammation of blood vessels)
Membranoproliferative glomerulonephritis (inflammation of the filters, called glomeruli, in the kidney)
Sialadenitis (immune disorder that destroys tear glands and salivary glands)
Probable association (moderate evidence to support a potential association between the condition and hepatitis C):
Porphyria cutanea tarda (skin condition in which blisters appear in exposed parts of skin)
Suspected association (some evidence for an association but not sufficient to strongly link the condition with hepatitis C):
Autoimmune thyroid disease
Autoimmune thrombocytopenia (blood disorder with low platelet counts)
Cancer of the lymphatic system (non-Hodgkin's lymphoma)
Mucosa-associated lymphoid tissue (MALT) lymphoma (lymphoma of the mucosal lining of the stomach and other mucous membranes, including those of organs such as the salivary glands, thyroid, and lungs)
Lichen planus (skin condition in which bumps appear on the skin; can involve oral mucosa, genitals, and nails)
Hyde's prurigo nodularis (multiple skin nodules and intense itching)
Mooren's corneal ulcer (painful ulceration of the cornea; a rare condition)
Idiopathic pulmonary fibrosis (lung tissue scarring without a known cause)
Diabetes
CREST syndrome (cutaneous form of scleroderma)

important to note that most of these conditions can occur without hepatitis C infection and also can occur randomly in people who have hepatitis C.

A detailed description of the mechanisms of diseases that can occur outside the liver is beyond the scope of this discussion, but an understanding that individuals who have hepatitis C may also have some of the conditions described here is important. This knowledge could help in discussing with a physician the possibility of an association with hepatitis C.

Although there are many conditions that are suspected to have an association with hepatitis C, only a few have a proven association. How hepatitis C causes these diseases (that is, the precise mechanism) is not known.

It has been suggested that some of these conditions are caused by abnormal B-cell proliferations (examples are membranoproliferative glomerulonephritis, lymphoma, cryoglobulinemia, leukocytoclastic vasculitis, and MALT lymphoma) or by autoimmunity (examples are Behcet's syndrome, Hyde's prurigo nodularis, Mooren's corneal ulcer, and lichen planus). Sialadenitis, thyroiditis, thrombocytopenia, and other conditions such as porphyria cutanea tarda remain poorly explained. The list of potential associations is long, and only the conditions for which there is strong or moderately strong evidence for an association are further described in this chapter. Again, keep in mind that many of these conditions can occur in the absence of hepatitis C infection. For more about many different skin conditions, the Internet has a wealth of information and pictures.

Many of these conditions improve or remain unchanged after hepatitis C treatment, but in many studies, hepatitis C was treated with interferon only (monotherapy), leading to low cure rates, and that may partially explain the inconsistent results. It is possible, however, that many of these conditions are directly related to hepatitis C infection. The response to interferon treatment, as reported in the studies, is summarized in table 9.2. The responses were inconsistent across different studies, and some studies did not clearly report response. Because hepatitis C treatment has improved dramatically, with cure rates of more than 90 percent,

Table 9.2. Response to Interferon-Based Treatment in People with Extrahepatic Manifestation of Hepatitis C

Condition	*Response to Alpha-interferon*
Cryoglobulinemia and vasculitis	Improved or no change
Glomerulonephritis	Improved or no change
Non-Hodgkin's lymphoma	Improved
Lichen planus	Improved, no change, or deterioration
Mooren's corneal ulcer	Improved
Porphyria cutanea tarda	Improved or not reported
Thrombocytopenia	Deterioration
Thyroid dysfunction and/or anti–thyroid peroxidase (anti-TPO) antibodies	Deterioration or no change

we may now find better response rates, if indeed these conditions are strongly linked to hepatitis C infection.

In addition to the conditions named above, people with hepatitis C can sometimes develop autoantibodies (as detected by blood tests) to other organs; however, the relationship between autoantibodies and disease is weak. The commonly seen antibodies include rheumatoid factor (occurring in rheumatoid arthritis), anti-nuclear antibody (in lupus), anti–smooth muscle and anti–liver-kidney microsomal antibody (in autoimmune hepatitis), anti–neutrophil-cytoplasmic antibody (with inflammatory bowel disease or sarcoidosis), anti-thyroid antibody (with thyroid disease), and anti-cardiolipin antibody (with many conditions, including anti-phospholipid syndrome, and associated with blood clots, fetal loss, and low platelets). Often, these antibodies do not indicate actual disease and may lead to an incorrect diagnosis if the physician has not diagnosed the person with hepatitis C.

Essential Mixed Cryoglobulinemia

The most common and proven condition that occurs in association with hepatitis C infection is mixed cryoglobulinemia. A person affected with this condition has proteins (called cryoglobulins) in the blood that thicken

Table 9.3. Clinical Signs and Symptoms of Cryoglobulinemia

Joint pain (arthralgia)
Purple spots on the skin (purpura)
Weakness
Kidney disease (glomerulonephritis)
Numbness and tingling in hands and feet (peripheral neuropathy)
Inflammation of blood vessels (vasculitis)

(precipitate) at cold temperatures only. The proteins consist of immune factors that originate from more than one cell line (that is, are polyclonal). Table 9.3 outlines the signs and symptoms of this condition.

There are three different types of essential mixed cryoglobulinemia. Types II and III are most commonly found in people who have hepatitis C. In type II, the proteins come from a single cell line (are monoclonal), and in type III, the factor comes from more than one cell line (polyclonal). Because monoclonal or polyclonal B-lymphocyte multiplication is responsible for cryoglobulin production, essential mixed cryoglobulinemia may be related to a disorder in which too many white blood cells are produced (hepatitis C–associated lymphoproliferative disorder). Approximately 5 to 8 percent of people with this disorder will develop B-cell lymphoma (malignant tumor of the lymph system).

Rarely, cryoglobulinemia involves more than one organ and may be life-threatening, especially with severe inflammation of blood vessels (vasculitis). In rare cases, this condition may involve leakage of fluid into the covering of the heart (pericardial effusion) or into the covering of the lungs (pleural effusion).

More than 50 percent of people who have cryoglobulinemia respond to interferon treatment, with improvement in blood vessel inflammation and kidney function. Unfortunately, approximately 80 percent of those who respond to treatment with interferon will eventually suffer a relapse in the absence of cure of their hepatitis C infection. We do not know whether the treatment response will be higher with the newer, direct-acting antiviral medications, but it is likely that it will.

Membranoproliferative Glomerulonephritis

People with both membranous and membranoproliferative glomerulonephritis, a type of kidney disease in which the filters (called glomeruli) in the kidney are inflamed, are more likely to have hepatitis C infection than individuals who have other types of kidney disease. Individuals who have glomerulonephritis are routinely tested for hepatitis C infection. Membranoproliferative glomerulonephritis can occur with or without cryoglobulinemia.

Glomerulonephritis is a common result of essential mixed cryoglobulinemia and occurs in as many as 50 percent of people with the latter disease. If this condition is suspected, the physician will perform a kidney biopsy. Individuals who have glomerulonephritis may not have other symptoms of chronic liver disease.

People who have membranoproliferative glomerulonephritis usually have a large amount of protein in the urine (measured by the collection of urine for 24 hours) and have mild to moderate renal insufficiency (as assessed by the severity of elevated serum creatinine levels). Approximately 60 to 70 percent of individuals with this condition may have detectable cryoglobulins in their blood. If a liver biopsy is performed, it may show moderately severe chronic hepatitis with or without cirrhosis. It has been suggested that deposits of proteins (which may contain hepatitis C virus, cryoglobulins, and other antibodies) in the small blood vessels (the capillaries) of the glomeruli of both kidneys cause this type of kidney disease.

Studies show that treatment of hepatitis C infection will improve membranoproliferative glomerulonephritis. This evidence supports the hypothesis that this condition may be caused by the hepatitis C infection. The treatment response could be further tested with the improved hepatitis C treatment regimens that are currently available.

Inflammation of Salivary Glands (Sialadenitis)

People who have hepatitis C may develop an inflammation of the salivary glands, called sialadenitis, and this condition is frequently seen with

cryoglobulinemia. Although similar inflammation of salivary glands is also seen in Sjögren's syndrome, these two conditions are considered distinct. Sialadenitis that occurs with hepatitis C infection is considered part of the hepatitis C–related proliferation of lymphocytes. The presence of this condition may increase the person's risk of malignant lymphoproliferative disease, such as B-cell non-Hodgkin's lymphoma.

Porphyria Cutanea Tarda

Porphyria cutanea tarda is a general term used for a skin condition caused by deposits of a chemical called porphyrin in the skin, making the skin sensitive to sunlight. It can be a genetic (inherited) disorder or an acquired condition. Porphyrins are produced during the synthesis of heme (a component of hemoglobin, the molecule that carries oxygen in red blood cells), and the disease results from a deficiency in an enzyme (called uroporphyrinogen decarboxylase) that results in overproduction of porphyrins.

A person who has this disease typically has increased skin fragility and develops fluid-filled sacs or lesions (called vesicles and bullae) on areas of the skin that are frequently exposed to the sun (usually the back of the hands or forearms), which leads to skin discoloration or scarring with the formation of small white bumps (called milia). Different manifestations of this skin condition include thick hair growth on the face and body, dark spots, and thickened skin that develops over a period of time. Typically, the disease affects middle-aged men who drink alcohol excessively and have symptoms of liver disease and iron overload. However, this condition is also associated with hepatitis C infection.

Although porphyria cutanea tarda can occur in people who do not have hepatitis C, there is a high rate of prevalence of hepatitis C in individuals who have this condition. In some countries, including Spain, Italy, and southern France, nearly 70 to 90 percent of people who have porphyria cutanea tarda also have hepatitis C infection. In the United States, approximately 50 percent of people who have this condition also have hepatitis C. Despite this strong association, the exact mechanism by which hepatitis C causes porphyria cutanea tarda remains unclear.

The conventional treatment for porphyria cutanea tarda is to repeatedly remove blood to reduce the amount of iron in the body to the point of mild iron deficiency. For people who have hepatitis C infection, additional treatment of hepatitis C should be considered. In addition, all people who have porphyria cutanea tarda should avoid drinking alcohol and taking estrogen supplements (either hormone replacement pills or contraceptive pills).

Lichen Planus

Lichen planus is a benign disease characterized by itchy bumps on the skin. These bumps may be violet in color and may appear on wrists, ankles, and genitals and in the mouth. This condition is believed to be caused by proliferation of T lymphocytes.

The association between lichen planus and hepatitis C infection was first reported in 1991. The prevalence of hepatitis C in people who have lichen planus varies considerably from one geographic area to another; it is high in some countries (for example, about 60 percent in Italy and Japan), but in other countries (the United Kingdom), no such association has been found.

Although the precise role of hepatitis C in lichen planus remains unclear, any individuals who have lichen planus and have liver disease or painful sores in their mouth should be tested for hepatitis C. If the person is diagnosed with hepatitis C infection, the physician will try to cure the infection.

In the past, some people receiving interferon treatment experienced a worsening of lichen planus. The sudden onset of lichen planus has also been reported in some people who have chronic hepatitis C and are undergoing treatment with alpha-interferon. With the more effective hepatitis C treatments now available, the outcome of this condition may improve. We may also be able to confirm whether there is a strong association between hepatitis C and lichen planus, because most people who have hepatitis C can be cured without using interferon.

Thyroid Disease

There may be an association between autoimmune thyroid disease and hepatitis C infection. Studies have documented a high prevalence of thyroid antibodies in people who have chronic hepatitis C infection. These individuals may be particularly susceptible to the development of Hashimoto's thyroiditis (a condition in which the thyroid is damaged by the immune system) after treatment with alpha-interferon. Both underactive thyroid (hypothyroidism) and overactive thyroid (hyperthyroidism) have been observed in people treated with alpha-interferon, and the latter condition frequently evolves into hypothyroidism. People already receiving thyroid replacement therapy may require an increase in dosage during interferon therapy and a decrease once therapy with alpha-interferon is completed. For this reason, the physician needs to closely monitor thyroid function in all people considering treatment with alpha-interferon.

Non-Hodgkin's Lymphoma

Several reports, particularly from studies in southern Europe, have suggested an association between hepatitis C infection and non-Hodgkin's lymphoma. The development of non-Hodgkin's lymphoma among people who had hepatitis C infection was seen most frequently in association with cryoglobulinemia. The rate of prevalence and detection of lymphoma in organs other than the lymph nodes was higher in people who were older and female. Survival and tumor response to chemotherapy did not differ between people who had hepatitis C and those who did not.

Some earlier studies had suggested that hepatitis C infection is associated with B-cell lymphoproliferative disorders that may evolve into non-Hodgkin's lymphoma. Hepatitis C is probably involved in the cause of this complication as more than just a risk factor.

Other Extrahepatic Manifestations

Several other conditions, including idiopathic pulmonary fibrosis, cutaneous necrotizing vasculitis, polyarteritis nodosa, Mooren's corneal

ulcer, idiopathic thrombocytopenia, diabetes, Behcet's syndrome, and CREST syndrome (a skin manifestation of scleroderma), have been described in association with hepatitis C infection, but no studies have proven that hepatitis C is the cause. An increasing number of studies find a relationship between type 2 diabetes and hepatitis C infection. However, because both conditions are common, it is difficult to prove a cause-and-effect relationship.

10

Co-infection with HIV and Hepatitis C

Because hepatitis C and HIV are blood-borne infections, both diseases are spread through contact with an infected person's blood. Therefore, it is common for individuals to be infected with both the hepatitis C virus and HIV. Worldwide, approximately 40 million people have HIV, and of those, between 4 and 5 million also have hepatitis C. In the United States, between 25 and 33 percent of those who have HIV—approximately 150,000 to 300,000 people—also have hepatitis C.

With the availability of effective HIV treatments, such as highly active antiretroviral therapy (HAART), hepatitis C–related liver disease has emerged as a major cause of death among people who have HIV. The 10-year survival rate for people taking HAART is nearly 90 percent, reinforcing the importance of treating hepatitis C in people who have HIV. This chapter presents important information about the common ways in which HIV and hepatitis C are spread, differences in the progression of hepatitis C in people who have HIV and those who do not, and treatment-related considerations for people who have both diseases.

Prevalence and Transmission of Hepatitis C in HIV-Infected People

Both HIV and hepatitis C are spread through exposure to infected blood and blood products, and having both infections increases the risk of spreading hepatitis C. The following are common direct ways of spreading both viruses:

- Sharing intravenous drug needles with an infected person
- Being exposed to contaminated blood or blood products, including through needle-stick exposure
- Having unprotected sex with an infected person
- Sharing toothbrushes or razors with an infected person
- Being the child of a woman who had both HIV and hepatitis C during pregnancy

Among people who have HIV and use intravenous drugs, between 60 and 90 percent have hepatitis C. In contrast, intravenous drug use was reported by between 15 and 30 percent of people who had only HIV. Among people who contracted HIV through contaminated blood products, approximately 50 to 70 percent have hepatitis C. The risk of transmission for each needle-stick exposure is tenfold higher for hepatitis C than for HIV (1.8 versus 0.3 percent).

The rate of hepatitis C infection is low (7 to 14 percent) in people who became infected with HIV through sexual modes. The low prevalence of hepatitis C among sexual partners of people who have HIV indicates the low transmission rates of hepatitis C through sexual exposure. However, to further prevent the spread of HIV and hepatitis C, people infected with both diseases should use condoms during sexual intercourse.

Rates of transmission of hepatitis C from a mother with only hepatitis C to her infant range from 4 to 7 percent per pregnancy. If a mother has both HIV and hepatitis C infections, the rate of transmission of the hepatitis C virus to the infant increases twofold to fourfold. How and when the virus is transmitted during pregnancy or birth is not well understood. Women should not have cesarean sections merely to prevent transmission of either of the viruses to their children.

Other safe practices, such as not sharing toothbrushes and razors, are also extremely important to prevent transmission to other people living in the same household.

Diagnosing Hepatitis C Infection in People Who Have HIV

All HIV-infected individuals should be tested for hepatitis C with the hepatitis C antibody test. Because people who have AIDS (that is, CD4 counts of less than 100/mm^3) or an early acute hepatitis C infection may not have hepatitis C antibodies, the physician should confirm the antibody test results using the hepatitis C RNA PCR test. Individuals at high risk of hepatitis C infection should be tested routinely with a PCR test to detect the hepatitis C RNA, even if hepatitis C antibodies are not present.

Because liver enzyme tests cannot adequately assess the severity of liver disease, people who have both HIV and hepatitis C should have a liver biopsy done so that the physician can assess the severity of liver disease. People who have cirrhosis should be screened for liver cancer by having blood tests every three to four months to measure their alpha-fetoprotein levels and should have yearly computed tomography (CT) scans or ultrasound examinations. The physician will carefully monitor any liver damage with more frequent blood tests and CT scans.

Effect of HIV Infection on Hepatitis C

For many people, HIV infection worsens hepatitis C–induced liver disease, especially in those who have low CD4 counts. For people who have acute hepatitis C, HIV infection decreases the likelihood of spontaneous clearance of the hepatitis C virus from 15 to 30 percent to 5 to 10 percent. And for those who have chronic hepatitis C infection, HIV infection causes higher hepatitis C viral counts and faster progression to liver disease.

Data from many studies show that the risk of developing cirrhosis is twice as high for individuals who have both diseases. Research also shows a much shorter time to develop cirrhosis in people who have both diseases than in those who have only hepatitis C (7 years versus 23 years). Similarly, the risk of death from liver disease is higher in co-infected individuals.

Some evidence suggests that the severity of fibrosis at the time of diagnosis may predict a person's risk of future liver-related complications and death. Compared with individuals who do not have fibrosis, people who have fibrosis have higher complication rates, and this risk seems to increase with the severity of fibrosis (it is greatest among people who have cirrhosis and lowest among those who have mild fibrosis).

People who have hepatitis C and HIV should not drink alcohol; the disease can progress more rapidly in individuals who drink.

Some people who have HIV and hepatitis C may also have hepatitis B. Therefore, it is a common practice to test people who have HIV for both hepatitis C and hepatitis B. Similarly, individuals who have hepatitis C are tested for both HIV and hepatitis B. Co-infected individuals should be immunized with hepatitis B and hepatitis A vaccines, because people who have hepatitis C are likely to have a worse prognosis if they also have hepatitis A or B.

The effect of HAART on hepatitis C is not well understood. Some studies show that people receiving HAART have increased hepatitis C RNA levels and CD4 counts, but these studies are not conclusive. Other studies report that people taking protease inhibitors or HAART for HIV show an improvement in liver disease (both inflammation and scarring). Moreover, people undergoing treatment for HIV have shown lower liver-related complication rates when compared with people who do not take treatment for HIV.

Table 10.1 summarizes the factors that affect hepatitis C progression in HIV-infected people.

People who have HIV are surviving longer because of HAART, and thus a significant number of people who have HIV are now dying of complications from advanced liver disease, including liver cancer. Once cirrhosis develops, co-infected people have a sixfold higher risk of developing abdominal swelling (ascites), mental confusion (hepatic encephalopathy), and bleeding from blood vessels (variceal bleeding) compared with people who have only hepatitis C. Therefore, it is extremely important for co-infected people to receive aggressive treatment for their hepatitis C infection.

Table 10.1. Factors Associated with Rapid Progression of Hepatitis C–Associated Liver Disease in People Who Have HIV

Low CD4 counts
No protease inhibitors or HAART therapy
Older age (more than 50)
Alcohol consumption (any)
Presence of active hepatitis B infection

Effect of Hepatitis C Infection on HIV

Although HIV infection adversely affects the natural progression of hepatitis C disease, the presence of a hepatitis C infection does not seem to affect the progression of HIV disease. Some study results suggest that hepatitis C infection may lead to rapid progression of HIV disease and its complications, but most experts believe that hepatitis C infection has little impact on HIV disease. Moreover, some suggest that when rapid progression of HIV is found in individuals who also have hepatitis C, it is probably related to ongoing intravenous drug use.

Because HIV antiretroviral treatments are known to cause liver damage, treatment of HIV in co-infected people may need to be adjusted because of the higher risk of liver damage in these individuals. Liver damage is more commonly seen with the HIV antiretroviral medication ritonavir, but similar problems have been observed, although with less frequency, with other HIV medications. The mechanism by which these HAART medications cause more liver damage in individuals with hepatitis C–induced liver disease remains unknown, but it may be due to the liver's decreased ability to eliminate the HIV antiretroviral medications. Physicians regularly monitor liver test results, such as liver enzymes and bilirubin, in all co-infected people undergoing treatment with antiretroviral therapy for HIV. Because the benefit of HIV treatment outweighs the risks, all individuals who have HIV and hepatitis C should consider treatment of their HIV infection.

Treatment of Hepatitis C in People Who Have HIV

Until recently, the results of hepatitis C treatment in people who have HIV have been suboptimal, with cure rates lower than for individuals infected with only hepatitis C. With the introduction of more effective hepatitis C treatments, the cure rates have improved for people who have HIV. The guidelines for treating co-infected individuals are that, in general, all people who have HIV should be considered for hepatitis C treatment if there are no obvious reasons that treatment should not be given (table 10.2).

The treatment of hepatitis C in people who have HIV is discussed in more detail in later chapters and is only broadly outlined here.

In one study, people who had both hepatitis C and HIV had a lower cure rate than people who had only hepatitis C (the cure rate was 10 to 15 percent lower). Data from several studies show cure rates of 25 to 35 percent for people who have hepatitis C genotype 1 and HIV and are treated with a combination of pegylated interferon and ribavirin, compared with 40 to 50 percent for people who do not have HIV. People

Table 10.2. Treatment for Hepatitis C in People Who Have HIV

Who should receive treatment for hepatitis C?
People who have any evidence of scar tissue (fibrosis) on liver biopsy
People who have cirrhosis without complications
People who have high CD4 counts and are not currently receiving antiretroviral therapy
People who are receiving antiretroviral therapy
Who should not receive treatment for hepatitis C?
People who have complications of cirrhosis, such as fluid in the abdomen (ascites), confusion (encephalopathy), or bleeding from blood vessels in the organs (variceal bleeding)
People who have significant anemia (low hemoglobin), low white blood cells, and low platelets
People who have advanced AIDS
People who are actively using intravenous drugs and/or alcohol

Table 10.3. Treatment Response of People Who Are Co-infected with HIV and Hepatitis C Genotype 1 Virus

Treatment	*Cure Rates for Hepatitis C*
Interferon alone (48 weeks)	~16%
Interferon + ribavirin (48 weeks)	~25%
Pegylated interferon + ribavirin (48 weeks)	~33%
Pegylated interferon + ribavirin + boceprevir (48 weeks)	63%
Pegylated interferon + ribavirin + telaprevir (48 weeks)	74%
Pegylated interferon + ribavirin + simeprevir (24 to 48 weeks)	79%
Pegylated interferon + ribavirin + sofosbuvir (12 weeks)	89%
Sofosbuvir + ribavirin (no interferon for 24 weeks)	76%
Interferon-free oral medications (12 weeks)	~95%

infected with hepatitis C genotypes 2 or 3 have high response rates to treatment. The reported cure rates based on small studies of people with the genotype 1 virus are shown in table 10.3.

The lower response rate in people who have HIV and hepatitis C is partly because co-infected individuals usually have more advanced liver disease and, because of anemia, are unable to tolerate the optimal dose of ribavirin. Newer, direct-acting oral medications appear to have similar cure rates for people who have HIV and for those without HIV.

Special considerations for therapy for people who have both HIV and hepatitis C can be summarized as follows:

- All people who have HIV and hepatitis C should be considered for HIV treatment, irrespective of CD4 counts.
  - The only exception may be individuals who do not have any fibrosis, because they could wait for less expensive treatments in the near future.
- A physician will consider possible drug interactions with HIV medications when hepatitis C treatment is initiated.
- People who are newly diagnosed with HIV and hepatitis C could consider hepatitis C treatment, if their CD4 counts are high (more

than 500/mm^3), before initiating treatment for HIV, thus avoiding any potential drug interactions.

In general, most people who have HIV can be successfully treated for hepatitis C under the careful guidance of a physician with expertise in both HIV and hepatitis C.

Management of Advanced Liver Disease in People Who Have HIV

People who have advanced cirrhosis and HIV should seek the expertise of a liver specialist. Treatment of hepatitis C may carry major risks for these individuals, and they may not tolerate or may not respond to hepatitis C treatment.

People who have advanced liver disease may require a liver transplant. Whether people who have HIV and hepatitis C should receive a liver transplant is an area of controversy, but these views are slowly changing in favor of transplantation, given the introduction of more effective hepatitis C treatments. Many centers are now considering liver transplantation for certain people who have both HIV and hepatitis C. Individuals should consult an expert transplant hepatologist to explore this option. Some studies show that individuals who have both hepatitis C and HIV have survival rates after transplantation similar to those for individuals who have only hepatitis C, but the results of these studies vary.

> People who have both HIV and hepatitis C are more likely to develop liver cancer than those with only hepatitis C. Screening for liver cancer is important for people with HIV who are co-infected with either hepatitis B or hepatitis C.

In the era of successful HIV treatment with HAART, people infected with both HIV and hepatitis C now live longer, and hepatitis C–related liver disease has become a major cause of illness and death. HIV infection accelerates the progression of hepatitis C–induced liver disease to cirrhosis, liver cancer, and death. All people who have both HIV and hep-

atitis C are encouraged to undergo a liver biopsy to assess the severity of liver disease and decide upon the best treatment. In general, all those who have both diseases should consider both HIV and hepatitis C treatments. A combination of the newer, direct-acting antiviral medications will cure hepatitis C in most people who have HIV, with fewer side effects. The optimal duration of treatment is not yet defined, but most likely will be 12 weeks. There are no clear guidelines regarding liver transplantation for co-infected people, but transplant physicians are showing an increasing interest in exploring this option for these individuals.

11

Acute Liver Failure

Liver failure occurs when the liver cannot perform some of its functions. Most often, liver failure occurs gradually over many years; however, in acute liver failure, the liver loses its function quickly, usually within six months and sometimes within a period of several days. Acute liver failure is a rare condition, but it can be associated with a fatal outcome. Approximately 2,000 cases of acute liver failure are reported in the United States every year. The number of people who have acute liver failure worldwide is between 1 and 6 per million and is more common in countries that have high rates of hepatitis A, B, and E infection.

People who experience liver failure can have any of the following signs and symptoms:

- Mental changes (hepatic encephalopathy), including irritability and confusion, caused by the liver's inability to eliminate toxins
- Bleeding easily, caused by the decreased production of blood clotting factors (measured as prothrombin time or as international normalized ratio, INR)
- Yellow discoloration of the eyes or skin (jaundice)

Young children who have acute liver failure are not likely to have hepatic encephalopathy.

Acute liver failure is divided into three subtypes:

- Hyperacute: encephalopathy within two weeks of the appearance of jaundice
- Acute: encephalopathy occurring 2 to 8 weeks from the appearance of jaundice
- Subacute: encephalopathy occurring 9 to 26 weeks from the appearance of jaundice

Causes

The causes and outcomes of acute liver failure may vary, depending on the subtype. Some of the possible causes are listed in table 11.1.

Acute liver failure is commonly caused by medications such as acetaminophen (Tylenol). In the United States, acetaminophen is becoming the most common cause of liver failure and usually occurs when a large amount of acetaminophen is consumed either intentionally or inadvertently. Those who use medications that contain both acetaminophen and narcotic drugs such as codeine to control pain may underestimate the amount of acetaminophen used. The FDA is attempting to reduce this risk by banning pain medications that are co-formulated with acetaminophen. It is important to note that acetaminophen is more likely to cause liver

Table 11.1. Possible Causes of Acute Liver Failure

Acetaminophen (Tylenol)
Other medications or herbal preparations
Hepatitis B
Hepatitis E (mostly in South Asia)
Autoimmune hepatitis
Hepatitis A
Ischemic hepatitis
Budd-Chiari syndrome (obstruction of hepatic vein blood flow)
Wilson's disease
Mushroom poisoning
Ischemic hepatitis
Tumor infiltration

failure in people who drink alcohol excessively; moreover, some people may underestimate the amount of acetaminophen consumed when they are under the influence of alcohol. Acute liver failure can occur in people who have hepatitis C and take more than the recommended dose of acetaminophen. Therefore, whether healthy or having liver disease, all individuals should avoid taking more than 2,000 mg (four 500 mg tablets or capsules) of acetaminophen in one day.

In addition to acetaminophen, many other medications, including nonsteroidal anti-inflammatory drugs (ibuprofen and similar drugs), antibiotics, antiseizure drugs, and anti-tuberculosis medications, can cause acute liver failure. However, these medications are the cause of acute liver failure in less than 10 percent of cases in the United States.

Viral hepatitis (hepatitis A, B, or E) or autoimmune hepatitis can also cause acute liver failure. Hepatitis B is a common cause of acute liver failure throughout the world, and in the United States, 1 in 10 cases of acute liver failure are believed to be caused by hepatitis B. In India and Pakistan, hepatitis E is the predominant cause of acute liver failure, occurring in almost half of the cases. Less than 5 percent of acute liver failure throughout the world is caused by hepatitis A.

Hepatitis C does not usually cause acute liver failure. However, because hepatitis A or B is more likely to cause acute liver failure in someone who already has a hepatitis C infection, individuals with hepatitis C should get vaccinated for hepatitis A and B.

Acute liver failure could also be caused by a lack of blood supply to the liver (a condition called ischemic hepatitis). This condition is more common in elderly individuals and people who have heart conditions. This type of acute liver failure is easy to diagnose because the person's liver enzymes increase rapidly (to 20 to 200 times normal levels or more; aspartate aminotransferase level is usually higher than alanine aminotranferase). In most people, after supportive treatment (intravenous fluid, oxygen, and medications to bring the blood pressure to the normal range), the enzymes rapidly return to normal levels. It is rare for these individuals to develop acute liver failure, despite a major elevation in liver enzymes, mainly because recovery is rapid after reversal of the ischemia.

After any major surgery, rapid development of liver failure in the immediate postoperative period is most commonly caused by rapid worsening of previously unidentified chronic liver disease. However, acute liver failure after surgery can be caused by a lack of blood flow to the liver or because of a toxic reaction to anesthetic agents or antibiotics.

The cause of acute liver failure can be identified in most people by asking them about their health history (medical conditions, recent travel, risk factors for viral hepatitis, medications, and alcohol use) and conducting certain blood tests and liver imaging. For approximately 20 percent of individuals, however, the cause of acute liver failure is not known. If a physician cannot identify the cause of the acute liver failure, or suspects the cause may be a treatable condition such as Wilson's disease or autoimmune hepatitis, the physician may perform a liver biopsy. However, most people who have acute liver failure will not require a liver biopsy. Because liver biopsy has significant risks for individuals who have acute liver failure (the risk of bleeding is very high because clotting abnormalities are common in acute liver failure), physicians will carefully consider all potential benefits and risks before deciding to do a biopsy. The information they obtain should be of some benefit in treatment.

Treatment for Specific Causes

Acute liver failure is an urgent condition that leads to failure of other organs (multi-organ failure). Early recognition of the cause of acute liver failure may help the physician to treat the cause and allow the liver to recover and heal on its own by regenerating new tissue (this can occur, for example, with autoimmune hepatitis, acetaminophen toxicity, or Budd-Chiari syndrome). Therefore, it is important to seek help from an experienced liver center for the best outcomes.

Specific treatment is based on the cause of acute liver failure. For causes not included below, there are no specific treatments.

Acetaminophen (Tylenol) A few toxins, including acetaminophen, can cause liver damage, depending on their dose. Acetaminophen causes the death of liver cells (hepatocellular necrosis), depending on the amount

taken. Early treatment using N-acetylcysteine (NAC) has been shown to improve the chances of recovery without a liver transplant.

Because of its low toxicity, the use of NAC is considered for all individuals who may have high levels of acetaminophen in their bodies. The physician will use a nomogram graph (a type of graphic calculator) to predict the levels of toxin in the blood at various time intervals after an overdose. The nomogram is not always reliable, however, because the exact time of ingestion may not be known or the person may take acetaminophen continuously or intermittently over a short time. In addition, even a lower dose of acetaminophen may be fatal in alcoholics and in people who take the drug after a period of prolonged fasting. Therefore, the physician may opt to treat the person with NAC even if the nomogram does not indicate potential liver toxicity.

NAC can be given by mouth or intravenously. The initial oral dose is 140 mg/kg of body weight, followed by 17 doses (70 mg/kg) at 4-hour intervals. The intravenous dose is 150 mg/kg over 60 minutes (in 5 percent dextrose), followed by 12 doses (70 mg/kg) at 4-hour intervals. Rarely, the intravenous route is associated with a severe allergic reaction (called anaphylaxis), which usually improves with antihistamines.

Mushroom Poisoning Mushroom poisoning is rare in the United States. The symptoms include nausea, vomiting, and diarrhea, and this may lead to electrolyte abnormalities. In addition to correcting the electrolyte and fluid abnormalities, specific treatment is also given. If mushroom (*Amanita phalloides*) poisoning is suspected, the recommended treatment is a combination of intravenous penicillin and silibinin, given together.

Wilson's Disease Wilson's disease is a genetic disorder resulting in the accumulation of copper in the liver and other organs. Usually, children are affected by this condition, and they may have signs of cirrhosis, including jaundice and abdominal swelling. This disease is one of the exceptions in which acute liver failure is diagnosed even in the presence of cirrhosis but the person may initially show signs of acute liver failure. Liver transplantation is the only treatment option for most people who have acute liver failure caused by Wilson's disease. Although substances that remove copper, such as penicillamine, trientine, or zinc, are not ef-

fective in many instances, the physician should try using these agents because they can be beneficial in a few select people who have acute liver failure. However, evaluating a person for a liver transplant should not be delayed while awaiting the results of treatment with these substances, because only a small number of people will be able to avoid undergoing liver transplantation.

Autoimmune Hepatitis People who have autoimmune hepatitis may initially show signs of acute liver failure. Usually, the onset of encephalopathy is delayed by weeks or months after the appearance of jaundice, and, often, the liver biopsy may show the presence of cirrhosis at the time of acute liver failure.

The physician may provide intravenous steroids to treat autoimmune hepatitis or give other medications to help suppress the person's immune system. Early diagnosis may avoid liver transplantation for many people who have autoimmune hepatitis. The presence of antibodies such as anti-nuclear antibody or anti–smooth muscle antibody, or simply a clinical suspicion, may lead the physician to do a liver biopsy. While waiting to see the response to steroids, the physician will assess whether the person is eligible for a liver transplant. The decision to do liver transplantation will be based on treatment response and the clinical judgment of the treating team.

Other Causes Acute liver failure caused by ingesting hydrocarbons such as carbon tetrachloride and trichloroethylene is infrequent in the United States. Carbon tetrachloride is a chemical used in some dry-cleaning agents and refrigerants, and trichloroethylene is an industrial solvent. Accidental ingestion or inhalation may result in a syndrome characterized by both liver and kidney failure. NAC has been used as an antidote for this condition, but its efficacy is not well established.

Antiviral treatments are not helpful for the management of acute liver failure caused by viral hepatitis. Rarely, hepatitis C may cause acute liver failure in people who have received a liver transplant, and in those situations, the newer antiviral medications may be effective.

In cases of acute Budd-Chiari syndrome, which is caused by blood clots blocking the hepatic veins that carry blood from the liver to the heart, the person has fluid in the abdomen, abdominal pain, and liver

failure. Medications that can dissolve the blood clots (thrombolytic therapy) may open the liver veins, relieve liver congestion, and reverse the acute liver failure.

Pregnancy-associated acute liver failure (acute fatty liver of pregnancy and HELLP syndrome, which includes blood cell breakdown, elevated liver enzymes, and low blood platelet count) usually resolves after delivery of the baby.

Prognosis

The survival rate for people who have acute liver failure can be influenced by the cause. People whose acute liver failure is caused by acetaminophen or hepatitis A have a better chance of survival than those who have acute liver failure for which the cause is unknown (presumably viral) or is caused by other medications. Individuals who have Wilson's disease and acute liver failure are also less likely to survive without liver transplantation.

When acute liver failure progresses in severity and people develop complications, such as brain swelling, coma, or uncontrolled infection (sepsis), the prognosis is poor and mortality is almost 100 percent. People who develop encephalopathy within a short period (less than two weeks) after developing jaundice have a better prognosis than people who develop encephalopathy more than two weeks after the appearance of jaundice.

When a person is experiencing acute liver failure, the decision about liver transplantation has to be made quickly. Physicians use a model to assess prognosis and thus the person's eligibility for liver transplantation, and many different prognostic models are available. The most commonly used model was developed at Kings College London (table 11.2). Prothrombin time or INR is a useful measurement to predict prognosis. The physician monitors the prothrombin time; an increased prothrombin time (more than 50 seconds) is a poor prognostic indicator. The models for acetaminophen and for other causes are different because of the better prognosis for people who have liver failure caused by acetaminophen.

Table 11.2. Prognostic Predictors for Acetaminophen-Induced and Non-Acetaminophen-Induced Acute Liver Failure

Blood Test Results and Clinical Signs	*Risk of Death without Liver Transplantation*
Acetaminophen-induced:	
Arterial blood pH less than 7.3	95%, even without any other risk factors
Prothrombin time more than 100 seconds (INR more than 6.5)	95%, if all three adverse factors present
Creatinine more than 3.4 mg/dl	
Coma (stage III or IV; see table 11.3)	
Non-acetaminophen-induced:	
Prothrombin time more than 100 seconds (INR more than 6.5)	95%, even without any other risk factors
Prothrombin time more than 50 seconds (INR more than 3.5)	80%, if one adverse factor present; 95%, if three or more adverse factors present
Creatinine more than 3.4 mg/dl	
Bilirubin more than 18 mg/dl	
Age less than 10 years or older than 40 years	
More than 7 days of jaundice before encephalopathy	
Unknown viral infections, drugs, toxins	

Tertiary Care Management and Liver Transplant Evaluation

Individuals who have acute liver failure are best treated in centers that have facilities for liver transplantation. The following information is intended for healthcare providers who treat people who have acute liver failure.

It is preferable to transfer the patient to a liver transplant facility before he or she goes into a coma. Helicopter transportation is preferable to traveling in a pressurized aircraft or by automobile because of the potentially damaging effects of depressurization (in air travel) and centrifugal forces (in road travel) on swelling of the brain.

The United Network for Organ Sharing's current rule permits people who have acute liver failure to be listed as "status I," ensuring that they have the highest priority on the transplantation waiting list.

The decision as to whether a person will survive without liver transplantation is made using prognostic models, as described above, and depends on the team's experience in managing cases of acute liver failure. However, even for the most experienced physicians, this decision is not an easy one. Hence, for all people who have acute liver failure, the physician will begin evaluation for a liver transplant if the prognostic models indicate a fatal outcome without a transplant. If the person's likelihood of survival is less than 20 to 30 percent, transplantation is the best option. The physician will not consider liver transplantation for people who have permanent brain damage, cancer, or bacterial or fungal infections.

Management of the Complications of Acute Liver Failure

As discussed above, acute liver failure leads to multi-organ failure. The optimal management of acute liver failure is best done by an experienced multidisciplinary team.

The energy requirement of someone who has acute liver failure is high. To meet this requirement, the physician will start the person on either intravenous or enteral (through the intestine) feeding or a combination of both. Enteral feeding is optimal because of the potential benefit in reducing bacterial migration from the intestines, but it may not be possible because of the paralysis of the small intestine (a condition called ileus) that occurs in many people.

The complications of acute liver failure include the following:

- Hepatic encephalopathy
- Brain swelling
- Metabolic complications, including hypoglycemia (low blood sugar), acidosis, and alkalosis

- Gastrointestinal bleeding
- Bacterial infections
- Clotting abnormalities
- Respiratory failure
- Circulatory complications
- Kidney failure

A detailed description of the management of these complications is beyond the scope of this chapter and is only briefly discussed here.

Hepatic Encephalopathy

Hepatic encephalopathy is mainly caused by the accumulation of toxins such as ammonia, leading to a change in mental status and brain swelling. This condition is diagnosed when the person becomes confused or irritable, and it can lead to a coma. Hepatic encephalopathy is arbitrarily classified into four stages, as shown in table 11.3.

Hepatic encephalopathy by itself is not usually lethal, but swelling of the brain can cause permanent brain damage. Precipitating factors for hepatic encephalopathy such as stomach or intestinal bleeding, electrolyte disturbances, and infections should be promptly treated. When the condition progresses to stage III or IV (coma), the physician may opt to put the patient on a ventilator to protect the airways and assist with adequate ventilation.

Some individuals who have acute liver failure may become agitated, which could be caused by increased pressure in the brain (intracranial pressure) or hepatic encephalopathy. A physician may prescribe short-

Table 11.3. Stages of Hepatic Encephalopathy

Stage	*Signs and Symptoms*
Stage I	Mental slowness, slurred speech, mild confusion, euphoria
Stage II	Inappropriate behavior, agitation, drowsiness
Stage III	Sleeps most of the time, but arousable; marked confusion
Stage IV	Coma

acting benzodiazepines in these situations. Use of sedatives may interfere with proper neurological assessment, however, so a physician will administer them only if necessary. In addition, in cases of severe agitation, the person may need to be temporarily paralyzed.

Brain Swelling

Uncontrolled brain swelling is the most common cause of death from acute liver failure. Physicians cannot rely on their clinical judgment alone to determine the extent of brain swelling; they should use direct monitoring with sensors that are surgically placed inside the skull to allow accurate measurement of the pressure in the brain. These sensors are placed by neurosurgeons, after assessing the risks and benefits of the surgery.

The physician's goal is to maintain the person's intracranial pressure at less than 20 mm Hg and the cerebral perfusion pressure (the difference between the intracranial pressure and the mean arterial pressure) at more than 50 mm Hg.

The treatment options for brain swelling include the use of mannitol, barbiturates, and hyperventilation. It may be best to avoid mannitol for people who have kidney failure, as it may cause an increase in intracranial pressure. For people who have kidney failure, dialysis or continuous arteriovenous hemofiltration should be done after mannitol infusion. Continuous infusion of barbiturate may be used when intracranial pressure remains elevated despite mannitol infusion. A diagnosis of irreversible brain damage should not be made while the person is in a barbiturate coma.

To avoid an increase in a patient's intracranial pressure, the intensive care team will take the following precautions:

- If endotracheal intubation is necessary, it should be done carefully without any trauma, as traumatic intubation will lead to a rapid increase in intracranial pressure.
- Frequent suctioning of the airways can increase intracranial pressure. The duration of suctioning should be limited to less than

15 seconds, and lidocaine solutions may be used to reduce the irritation.
- Hypoxia (low oxygen) and hypercapnia (an increase in carbon dioxide) should be avoided by promptly instituting assisted ventilation and using 100 percent oxygen while suctioning.
- Because low arterial pressure decreases the cerebral perfusion pressure, arterial pressure should be maintained to keep the cerebral perfusion pressure higher than 50 mm Hg (cerebral perfusion pressure = mean arterial pressure − intracranial pressure).
- Elevation of the patient's head and neck may modestly decrease intracranial pressure, and a 15 degree elevation is usually recommended.

Metabolic Complications

Hypoglycemia (low blood sugar) occurs in 40 to 50 percent of people who have acute liver failure. Blood glucose should be monitored every two hours. A continuous intravenous infusion of 10 to 20 percent dextrose is sufficient to prevent hypoglycemia.

During the early phases of acute liver failure, alkalosis (an increase in blood pH) may be common because of increased respiratory rate and vomiting. Development of acidosis (low blood pH) portends a poor prognosis and is often caused by lactic acidosis (accumulation of lactic acid) and kidney failure. Bicarbonate replacement may be necessary but is often ineffective. Treating the underlying cause of acidosis may be the most efficacious approach. Hypophosphatemia (low phosphate) and hypomagnesemia (low magnesium) are common, and both phosphate and magnesium need to be replaced constantly. Hyperkalemia (high potassium) is observed in people who have kidney failure or Wilson's disease (as a result of hemolysis) and should be corrected according to standard guidelines. Ultrafiltration (a type of dialysis) or hemodialysis should be used when necessary. Hypokalemia (low potassium) should be treated judiciously and not overcorrected.

Gastrointestinal Complications

Upper gastrointestinal bleeding is common and is most typically caused by gastric erosions (small ulcers in the stomach). An endoscopy is necessary to rule out other lesions, which are amenable to endoscopic therapy.

Infectious Complications

Sepsis (an overwhelming blood infection) is fairly common in people who have acute liver failure and is associated with a higher risk of death. The classical features of sepsis such as fever and leukocytosis (an increase in white blood cells) may be absent in people with acute liver failure. Conversely, fever and leukocytosis may occur as a result of ongoing hepatocellular necrosis (death of liver tissue) itself. Uncontrolled sepsis also affects individuals' survival after liver transplantation.

Bacterial infections are most commonly caused by *Staphylococcus aureus*, *Staphylococcus epidermidis*, and gram-negative bacilli. Pneumonia is the most common infection. Occult fungal infection, most commonly caused by *Candida*, is also frequent. Lactic acidosis, disseminated intravascular coagulation (the widespread clotting of blood in the blood vessels, which may cause multi-organ failures, as well as reduction of the proteins necessary for clotting, which may lead to bleeding at various sites), decrease in urine output without hypovolemia (low blood volume), and unexplained hypotension (low blood pressure) are signs of sepsis.

If infection is suspected, physicians should prescribe a broad-spectrum antibiotic even in the absence of any positive cultures. We recommend a combination of vancomycin and a third-generation cephalosporin and/or one of the fluoroquinolones.

Certain precautions can prevent infections in people who have acute liver failure. Vascular catheters should be changed every 72 hours. The Foley catheter may be discontinued in people who have been diagnosed with kidney failure and have no urine output (a condition called anuria).

Fungal infection is also common. A person who has persistent signs of uncontrolled sepsis, despite antibiotics, should be given antifungal treatment. It may be prudent for physicians to add fluconazole (an antifungal agent) to the antibiotic regimen for people who are in the hospi-

tal for more than one week and while they are taking broad-spectrum antibiotics.

Coagulopathy (Clotting Abnormality)

Correction of coagulopathy is not recommended, because this will interfere with the ability to determine prognosis using prothrombin time. Fresh frozen plasma is used only for people who have severe bleeding or preceding invasive procedures such as liver biopsy or placement of an intracranial pressure monitoring device. Large quantities of fresh frozen plasma may be required to correct coagulopathy even modestly, and this may precipitate pulmonary edema (fluid in the lungs) and increase the risk of brain edema. Exchange plasmapheresis (a process that removes plasma and retransfuses with new plasma) is usually effective for correcting coagulopathy to acceptable levels, and many centers perform this before invasive procedures. Vitamin K should be given to all patients (5 to 10 mg daily intravenously). Intramuscular injections should be avoided because of the risk of bleeding (hematoma). Disseminated intravascular coagulation may contribute to the coagulopathy. Thrombocytopenia (low platelets) is also common in people who have coagulopathy and is most commonly caused by disseminated intravascular coagulation or drugs. Platelet transfusion is recommended only when platelet levels are less than 10,000/mm^3 or if there are any signs of bleeding.

Respiratory Failure

Acute respiratory distress syndrome (fluid in the lungs) is seen in 30 percent of individuals with acute liver failure and requires assisted ventilation. Standard ventilatory settings are appropriate for people who have acute liver failure. The timing of intubation is controversial for people who have mild encephalopathy and are maintaining adequate oxygenation.

Circulatory Complications

The hemodynamic features of acute liver failure are similar to sepsis, with high cardiac output, low peripheral vascular resistance, and arterial

hypotension. Using colloids and norepinephrine (the preferred pressor agent—that is, an agent that increases blood pressure), the mean arterial pressure should be kept higher than 50 to 60 mm Hg. Maintaining pressure above 60 mm Hg or more may be critical for people with increased intracranial pressure so that a cerebral perfusion pressure of at least 50 mm Hg can be maintained.

Kidney Failure

Kidney failure in people who have acute liver failure is defined as having a urine output of less than 300 ml/day and a serum creatinine level of more than 3.4 mg/dl. Kidney failure can occur for a variety of reasons and often has more than one cause. Kidney failure is a sign of poor prognosis. It could be part of hepatorenal syndrome (failure of the kidneys due to liver disease, as discussed earlier), acute tubular necrosis resulting from drug toxicity or poor blood flow to the kidneys. Physicians caring for individuals with acute kidney failure should ensure that medications that may cause damage to the kidneys are avoided at all costs and that the person is given adequate fluids. For patients with established kidney failure, hemodialysis or other alternative methods of dialysis may be initiated.

Liver Transplantation

Before the advent of liver transplantation, the survival rate for people who had acute liver failure was between 10 and 20 percent. Liver transplantation has improved the survival rate considerably and is now the gold standard of treatment. The decision to perform a transplantation is based on many factors. The posttransplant survival rate for people who have acute liver failure is slightly lower than that for individuals who have chronic liver diseases, with an average survival between 60 and 70 percent.

Potential Alternatives to Conventional Liver Transplantation

For people who have acute liver failure, death is not caused by the liver's failing to regenerate but, rather, is the result of complications from

derangement of liver function. Unless the liver is chronically diseased (as in Wilson's disease), it regenerates to regain its original size and function. This led to the concept that if an effective alternative can be provided to maintain liver function while the native liver regenerates, individuals could be spared from lifelong immunosuppressive drugs and their long-term survival would improve. The alternatives to liver transplantation include an auxiliary liver transplant and artificial liver support.

With an auxiliary heterotopic liver transplant, a few segments of a donor's liver are placed in a heterotopic site (a site not near the location of the recipient's liver) without removing the diseased liver. The transplanted segments of donor liver help the person to wait through the critical period while the native liver regenerates. Once the native liver has regenerated, the transplanted segments of the donor's liver can be removed or left to atrophy (that is, to shrink by rejection). With auxiliary orthotopic liver transplantation, the left lobe of the recipient's liver is removed and is replaced with the left lobe of the donor's liver. Because of the significant risk of death from complications of the surgery, most liver centers have stopped using these procedures.

Transplantation (xenotransplantation) with livers from other mammals such as baboons or pigs is an interesting concept in theory but has not evolved in practice, for many reasons, including the potential risk of animal-borne infections. Transplantation of liver cells instead of the whole or part of the liver is another exciting development in this field of research, in which harvested liver cells from a donor are injected into the recipient's spleen and then travel to the liver. It has been used successfully in some people with inherited metabolic disorders. Despite its theoretical potential, this procedure has not been adopted in clinical practice and continues to remain experimental.

A bioartificial liver assist device is a support device outside the body that can perform some of the liver's functions, such as filtering and cleaning the blood, using either donor human or pig liver cells. Although these devices have the potential to be used as an important bridge to transplantation, the experience with them is mixed, and more research is needed before they could be used routinely.

Extracorporeal (outside the body) circulation of blood through a pig liver or human liver that is unsuitable for transplantation has been attempted in some transplant centers, with some success. The main difficulty with this kind of support for someone who has acute liver failure is maintaining a viable liver until the person recovers or receives a transplant. Advances in stem cell research may lead to better liver assist devices in the future.

12

Liver Cancer

Liver cancer (hepatocellular carcinoma, or hepatoma) is one of the most common cancers in the world. Worldwide, it causes more than 1.3 million deaths every year (approximately 10 percent of all deaths in adults).

The number of new cases of liver cancer varies with geographic location, because of regional differences in the prevalence of risk factors such as hepatitis B and C. In the Western Hemisphere, liver cancer occurs in fewer than 2 in 100,000 people; however, in the United States and parts of Europe, the number of liver cancer cases is increasing because the number of people who have hepatitis C infections is increasing. In the United States, the number of new cases of liver cancer is higher in people of East Asian origin because of their higher rate of hepatitis B. In some parts of Africa, where hepatitis B and the cancer-causing fungal products called aflatoxins are common, and in East Asia, where hepatitis B is prevalent, between 40 and 60 people per 100,000 have liver cancer. However, the number of new cases in East Asia is decreasing because of widespread immunization for hepatitis B.

Liver cancer is more common in men (twofold to fourfold higher) than in women. The risk of liver cancer increases with age, with the risk peaking at approximately 50 years in areas of high incidence and about 70 years in areas of low incidence. This difference in the peak age is a reflection of differences in the causes of cirrhosis.

Possible Causes

The two most important causes of liver cancer are hepatitis B and hepatitis C (table 12.1). In parts of China and Taiwan, 80 percent of liver cancers are caused by hepatitis B. People who have hepatitis B may develop liver cancer even in the absence of cirrhosis; for most other causes, liver cancer is usually seen only in the presence of cirrhosis. In the United States and Europe, hepatitis B and C contribute equally. In Japan, where the numbers of new cases of hepatitis B and C are similar, the incidence of liver cancer is higher for hepatitis C than for hepatitis B (10.4 percent versus 3.9 percent). The incidence of liver cancer in people who have hemochromatosis could be as high as 45 percent.

The mechanism that causes liver cancer in people who have hepatitis B may involve either increased cell turnover resulting from chronic liver disease or a combination of processes specific to hepatitis B. These processes may include the hepatitis B DNA being integrated into the person's DNA, which disrupts the regulatory elements of cell cycling (the natural cycle of cell growth and division), or proteins produced by hepatitis B stimulating genes that may cause liver cancer. The pathogenesis of liver cancer in people who have hepatitis C is less understood. It is possible that some people who have hepatitis C had previous exposure to hepatitis B.

Table 12.1. Causes of Liver Cancer

Common causes:
Hepatitis B
Hepatitis C
Hemochromatosis
Aflatoxins
Less common causes:
Cirrhosis from any cause
Alcohol
Anabolic steroids

Other factors that can cause liver cancer include cancer-causing toxins (aflatoxins), alcohol, hemochromatosis (a condition that causes too much iron to accumulate in organs in the body), and anabolic steroids. In certain regions of Southeast Asia and sub-Saharan Africa, exposure to aflatoxins is common. These toxins are produced by two types of fungi found in grains, nuts, and seeds, and the grains get contaminated with these fungi because of poor storage facilities. Hepatitis B is also very common in these areas. The relative contributions of aflatoxins and hepatitis B to the cause of liver cancer in these parts of the world are poorly understood. However, a combination of aflatoxins and hepatitis B causes a high incidence of liver cancer in parts of sub-Saharan Africa.

For people with hepatitis C infection, alcohol has been found to be another risk factor for developing liver cancer. Whether this relationship is related to more aggressive disease caused by a combination of hepatitis C and alcohol or whether alcohol is an independent risk factor remains unknown. Obesity has also been shown to increase a person's risk of developing liver cancer. Among people who have hepatitis C infection, 5 percent develop liver cancer during their lifetime. However, the risk appears to increase with severe cirrhosis. Approximately 15 percent of people who have cirrhosis and hepatitis C will develop liver cancer during their lifetime.

The cirrhosis, irrespective of the cause, is a predisposing risk factor for the development of liver cancer. In a given population, the risk is three to four times higher for people who have cirrhosis than for people who have chronic hepatitis without cirrhosis.

The increased rates of cancer in individuals who have cirrhosis may be due to chronic inflammation. Increase in liver cell proliferation may lead to activation of cancer-causing genes (called oncogenes) and mutation of other types of genes called tumor suppressor genes. These changes, in turn, may initiate the development of liver cancer. In areas of low incidence of liver cancer, more than 90 percent of people who have liver cancer have underlying cirrhosis. However, the prevalence of cirrhosis is less (about 80 percent) in high-incidence areas where hepatitis B is commonly transmitted from mothers to infants.

Table 12.2. Screening for Liver Cancer

Who should undergo screening?
People who have hepatitis B (even in the absence of liver disease)
Anyone who has cirrhosis or very advanced fibrosis from any cause

Screening

Since early detection of liver cancer leads to better treatment and cure rates, it is important for those who have a higher risk of liver cancer to undergo periodic screening (every six months) (table 12.2). The screening should be done by liver scans and blood tests (testing for alpha-fetoprotein, AFP). Some physicians do not check AFP, because a third of people with liver cancer may have normal AFP levels (false-negative results) and mild increases in AFP levels are seen in the absence of liver cancer (false-positive results). Liver scans can be done by ultrasound, CT, or MRI.

People with a previous history of liver cancer (treated by surgery, liver transplantation, or radiofrequency ablation) should also undergo careful surveillance (at three-monthly to six-monthly intervals), since recurrence rates are very high after liver resection and radiofrequency ablation.

Signs and Symptoms

In North America and Europe, many people who have liver cancer have no symptoms when they are diagnosed. When symptoms occur, they can include

- Weight loss (4.4 percent)
- Gastrointestinal bleeding (4.4 percent)
- Jaundice (2.6 percent)
- Abdominal pain (rare)

In Asian countries where there is a high incidence of cancer, about 75 percent of people who have liver cancer have a swollen abdomen (ascites) or experience discomfort.

When people visit their physicians because of symptoms, it is often a result of their underlying liver disease.

Diagnosis

Based on a person's signs and symptoms, a physician may conduct the following tests if liver cancer is suspected:

- Test for elevated alpha-fetoprotein (AFP) level
- Ultrasound scan
- Computed tomography (CT) or magnetic resonance imaging (MRI)

Alpha-fetoprotein levels are increased in approximately two-thirds of people who have liver cancer. The probability that a person has liver cancer is high when AFP levels are above 400 ng/ml; however, elevations of between 10 and 100 ng/ml are common in people who have chronic hepatitis. In addition, as noted above, because AFP tests can often yield a false-positive result (the result is positive in the absence of liver cancer) or a false-negative result (the result is negative but the person has liver cancer), some physicians have stopped using this blood test routinely for screening purposes.

All people with elevated alpha-fetoprotein levels should have imaging of their liver (ultrasound, CT, or MRI) to rule out liver cancer. In our experience, steadily rising AFP levels generally indicate the presence of liver cancer.

Alpha-fetoprotein levels can double in approximately 60 to 90 days; therefore, the physician may check AFP levels every three to four months in people who have cirrhosis and are at high risk of developing liver cancer. Certain tumors of the ovary and testes (in conditions called undifferentiated teratocarcinoma and embryonal cell carcinoma of the ovary

or testis) can give false-positive results, and the physician will consider these cancers as possible causes of elevated AFP levels.

In addition to measurement of AFP levels, people who are diagnosed with liver cancer are routinely screened for hepatitis B (testing for hepatitis B surface antigen protein or hepatitis B core antibody immunoglobulin protein), hepatitis C (using hepatitis C antibody test or hepatitis RNA by ELISA or PCR test), and hemochromatosis.

The physician will rule out spread of the disease to other parts of the body by doing a CT scan of the chest. If the physician has any doubt about the diagnosis, an ultrasound-guided biopsy will be performed. The risk of spreading liver cancer by the biopsy needle (cancer spreading along the skin track) is low.

Liver imaging and blood tests are not always successful in detecting liver cancer early, because these tests may not show evidence of cancer in up to one-third of people who have early liver cancer (they have a false-negative result). Despite the limitations of screening, it is important to screen all people who have established cirrhosis, irrespective of the cause of the cirrhosis, doing a liver ultrasound and checking AFP levels every six months, because early diagnosis may lead to better cure rates. Some physicians use CT or MRI for screening because these imaging tests are more sensitive than ultrasound. Moreover, the physician is often unable to optimally visualize the liver using ultrasound when the person is obese.

The diagnostic accuracy of various imaging tests depends on the expertise of the operator (especially with ultrasound), the sophistication of the equipment and technique, the presence of cirrhosis, and, most importantly, the size of the tumor. For small tumors (less than 2 cm), the diagnostic accuracy ranges between 60 and 80 percent, and it reaches 100 percent with large tumors. Of the imaging tests, CT and MRI scans have better accuracy than ultrasound examination, but these tests are more costly than ultrasound.

The physician determines the stage of the tumor by using the TNM classification of the International Union Against Cancer, using a dedicated CT scan or MRI. When there is suspicion of liver cancer on the

basis of alpha-fetoprotein or ultrasound, the physician may follow up with a CT or MRI scan.

Treatment

The optimal treatment of liver cancer depends on a variety of factors, including

- Tumor size, location, and number
- Severity of liver disease and presence and severity of cirrhosis
- Presence of tumor spreading outside the liver
- Relationship of the tumor to liver blood vessels
- Presence of other serious diseases
- The individual's general health
- The physician's expertise

Many curative treatments are available when cancer is diagnosed in its early stages, when the tumor is small and has not spread outside the liver. However, the average survival of people who have liver cancer and have symptoms is only two to three months, because these individuals already have advanced cancer by the time they have symptoms.

In general, liver cancer does not respond well to conventional chemotherapy and radiation therapy. The options for treatment of liver cancer include

- Liver transplantation
- Removing the tumor and part of the affected liver (surgical resection)
- Using high-energy radio waves to destroy the tumor (radiofrequency ablation)
- Freezing the tumor (cryotherapy)
- Blocking the tumor's blood supply and treating the tumor directly with chemotherapy (chemoembolization)
- Injecting the tumor with alcohol (percutaneous ethanol injection)

- Injecting the tumor with radioactive beads (intra-arterial radioembolization with yttrium-90 microspheres)
- Using medications (chemotherapy)

Treatments and their outcomes are summarized in table 12.3.

Liver Transplantation

For people who have advanced cirrhosis, the best treatment option is a liver transplant (if the person is a suitable candidate), because cure rates are high and recurrence rates are low (less than 10 percent) after liver

Table 12.3. Treatments for Liver Cancer

Treatment	*What Is Done*	*Results*
Liver transplantation	Replacing entire liver with a liver from an organ donor	5-year survival 60% to 75%
Liver resection	Surgical removal of tumor and surrounding liver	5-year survival 35% to 42%, but tumor recurrence is high (50% to 85%)
Radiofrequency ablation	Destruction of tumor by inserting a needle into the tumor and applying heat energy	5-year survival 35% to 50%, but tumor recurrence is high (50% to 85%)
Cryosurgery	Destruction of tumor by freezing the tumor (not commonly used)	Few data available, but may be similar to radiofrequency ablation
Percutaneous ethanol injection	Destruction of tumor by injecting concentrated alcohol directly into the tumor (not frequently used)	5-year survival 30% to 40%, but tumor recurrence is high (50% to 85%)
Transarterial chemoembolization	Blocking blood supply to tumor and injecting chemotherapy medicine directly into the tumor, using a catheter through the artery that feeds the tumor	Considered palliative, but a minority of individuals may be cured (less than 10%)
Intra-arterial radiotherapy	Injecting yttrium-90 into the tumor, using a catheter through the artery that feeds the tumor	Considered palliative
Chemotherapy	Giving an oral medication to block the tumor's ability to grow	Considered palliative

transplantation. To be eligible for and to be given priority for a liver transplant, the individual has to meet certain tumor criteria known as the Milan criteria, in addition to other criteria, as discussed in chapter 17. The Milan criteria include the following:

- If only one tumor, the tumor is smaller than 5 centimeters
- If more than one tumor but fewer than three tumors in the same lobe of the liver, the tumors are smaller than 3 centimeters
- No evidence of spread of tumor outside the liver
- No evidence of spread into a major blood vessel of the liver

People who fulfill these criteria have a five-year survival rate of 60 to 75 percent without any evidence of tumor recurrence. Those who have larger tumors or more than three tumors could also be considered for a liver transplant, but they have poorer outcomes; moreover, because of these poor outcomes, they will not be given priority for liver transplantation.

Surgery

Only 20 percent of people who have liver cancer are potentially eligible for their tumors to be removed by surgery. For individuals who do not have cirrhosis, surgery is the preferred treatment, but it is uncommon for people (except those with hepatitis B or children with the fibrolamellar type of liver cancer) to have live cancer without cirrhosis. If the person has cirrhosis and the liver disease is mild—that is, he or she has a low MELD (model for end-stage liver disease) score or Child A score—a physician may attempt to surgically remove the tumor. For people who do not have cirrhosis, the rate of death from surgery when performed by an experienced surgeon is less than 3 percent, but the rate increases to about 8 percent for people who have cirrhosis. The overall five-year survival rate after surgical resection is approximately 35 percent, but for people who have small tumors (2 to 5 cm) the rate is about 42 percent. Certain tumor characteristics lead to better cure rates, including having a well-defined tumor or a fibrolamellar type of tumor (the type usually seen in children), no blood vessel involvement, and a tumor smaller than

Table 12.4. Treatments for Individuals Who Are Not Candidates for Surgery or Liver Transplantation

Individuals who have one or more of the following conditions are not considered good candidates for surgery:
Advanced cirrhosis (Child B or C score, high MELD score)
Ascites (abdominal swelling)
Large varices (bleeding from blood vessels)
Hepatic encephalopathy (mental confusion)
Tumors that have spread outside the liver
Tumors that have spread to the hepatic blood vessels
Other serious heart or lung conditions
Individuals who are not eligible for surgery or liver transplantation should consider one of the following treatments instead:
Radiofrequency ablation
Cryosurgery
Transarterial chemoembolization
Intra-arterial yttrium-90 radiation
Chemotherapy with sorafenib (oral medication given twice daily)

5 cm. If the cancer is removed by surgery and cancer returns at a later date in the remaining liver, the person could be considered for liver transplantation if the transplant criteria are met.

Table 12.4 summarizes reasons for ineligibility for surgery or liver transplant, along with the alternative treatments, which are discussed in the following sections. With the exception of radiofrequency ablation, the alternative treatments listed in table 12.4 are not considered curative. However, there is a small chance of a cure with these treatment options, except for chemotherapy with sorafenib. The size, location, and severity of the liver disease are taken into account when these palliative treatment options are considered. Many of these options are considered as a "bridge to liver transplantation."

The general guidelines regarding the choice of treatment are given in table 12.5. Many factors are taken into consideration in choosing the optimal treatment. Multiple modalities may also be used for the same person.

Table 12.5. Tumor Size and Treatment Options for Liver Cancer

Tumor Size	*Treatment Options*
Small tumor(s) (usually less than 5 cm)	Liver transplantation Liver resection Radiofrequency ablation Alcohol injection Cryosurgery Transarterial chemoembolization
Large tumor(s) (5 cm or more)	Surgery (in the absence of cirrhosis) Transarterial chemoembolization Transarterial radiation (yttrium-90)
Tumor spread outside the liver (metastases) or into a major hepatic blood vessel	Chemotherapy with sorafenib (transarterial chemoembolization or yttrium-90 could be considered if tumor has spread into a blood vessel within the liver but has not spread outside)

Radiofrequency Ablation

Recent studies show that for small tumors, the cure rates after radiofrequency ablation are comparable to those after surgical resection. During radiofrequency ablation, a special type of needle is placed through the skin into the tumor under ultrasound or CT scan guidance, and the tumor is destroyed with heat, using radiofrequency waves. This technique has become popular recently and has become the treatment of choice for small tumors. Radiofrequency ablation can be done as a curative therapy or to slow down tumor growth while the person is waiting for a liver transplant. Like surgical resection, liver transplantation could be considered for tumor recurrence after curative radiofrequency ablation if transplant criteria are met at the time of the recurrence.

Percutaneous Ethanol Injection

Before radiofrequency ablation became popular, smaller tumors were treated with percutaneous ethanol injection (alcohol injection). With this technique, concentrated alcohol is injected into a liver tumor with a long needle, using ultrasound or CT guidance. This is a relatively inexpensive treatment option but requires multiple sessions. The five-year survival

rate for people treated with alcohol injection who have a single tumor of less than 5 cm and Child A cirrhosis is approximately 40 percent; for multiple tumors, the five-year survival rate is approximately 30 percent. These favorable results could be due partly to better patient selection (people with smaller tumors and therefore better prognosis) or perhaps to the dedication and expertise of the interventional radiologist.

Transarterial Chemoembolization

During transarterial chemoembolization (TACE), a tube is inserted into the artery that carries the oxygenated blood that feeds the liver tumor. An interventional radiologist performs this procedure with X-ray guidance and confirms the location of the tumor by injecting contrast dye into the tumor. Once the tube is advanced selectively into the feeding artery, the physician injects either a mixture of chemotherapy drugs or drug-eluting beads (particles impregnated with chemotherapy medication) into the tumor and also cuts off the arterial blood supply (using beads or gel foam) to the tumor. Some physicians prefer not to inject chemotherapy medications and instead just cut off the arterial blood flow (this procedure is known as transarterial embolization). Without arterial blood flow, a significant part of the tumor will die (undergo necrosis), but, unfortunately, some tumors are supplied by more than one arterial branch, or some cancer cells survive, leading to an inadequate treatment response or recurrence. TACE is considered a palliative treatment (slowing down tumor growth), not a curative treatment. It is often used as a bridge to liver transplantation or, occasionally, to make the person suitable for liver transplantation or surgical resection. The five-year survival rate after TACE is approximately 6 percent, which may reflect the advanced cancer in this population; a three-year survival of 47 percent for tumors smaller than 5 cm has also been reported.

Intra-arterial Radiation Therapy

Intra-arterial radiation therapy is often used for larger tumors. The technique is similar to TACE except that yttrium-90 is injected into the feeding artery and provides localized radiation to the tumor. Like TACE, intra-arterial radiation therapy is considered a palliative treatment.

Chemotherapy

Many chemotherapy drugs have been tested for liver cancer, usually with dismal results. Only one medication, sorafenib, has been approved by the U.S. Food and Drug Administration for the treatment of liver cancer. Sorafenib (Nexavar) is approved only for cases of advanced disease when other treatments are less likely to be effective, and it is considered a palliative treatment. In clinical trials, the drug has been shown to prolong life even in advanced cases where the tumor has spread outside the liver or into major liver blood vessels, but this drug does not cure liver cancer. Sorafenib is given to individuals as two pills (2×200 mg) twice daily on an empty stomach. The common side effects are rash (mostly on hands and feet), fatigue, diarrhea, and high blood pressure. Sorafenib is often used in combination with other treatment modalities, although there is no firm evidence of positive results.

A Team Approach

People who have liver cancer may have the best treatment results at a center that uses a team approach. In these centers, specialists in hepatology, surgery, liver transplantation, and interventional radiology discuss the person's case, and the team then advises the individual on the best treatment options. In the future, gene therapy and immunotherapy may become applicable in the management of liver cancer.

Prevention

Most people who have liver cancer go to their physician at a late stage of disease, too late for any effective treatment. Screening for liver cancer could improve outcomes by detecting small tumors earlier. To have a major impact on reducing the death rate from liver cancer worldwide, an inexpensive yet sensitive diagnostic tool and an equally effective treatment would have to be made available. To date, no such test is available.

Early detection of liver cancer is possible, however, for those who have high risks and undergo screening periodically, as discussed earlier. There

is some evidence that coffee consumption may reduce cancer risk in people with cirrhosis, and this is discussed in chapter 19.

Approximately 300 to 400 million people are carriers of hepatitis B. To be effective, screening should be directed toward these high-risk individuals, as well as people who have hepatitis C and hemochromatosis. Alpha-fetoprotein testing and ultrasound are neither inexpensive nor sensitive enough to be applicable to a large population, especially in low-income countries. Another strategy might be to screen only those people who have viral hepatitis and cirrhosis. However, in areas where liver cancer is common, more than 50 percent of people who have liver cancer have cirrhosis without any symptoms. Therefore, any screening method aimed at people who have cirrhosis will exclude more than 50 percent of these high-risk individuals. At a global level, screening may not have much of an impact.

Even in the most skilled surgeon's hands, surgical removal of the tumor gives a five-year survival of only about 40 percent. The surgical expertise necessary to obtain this survival rate is not available in many countries with high incidence rates. Therefore, early detection is not likely to have any major impact on the rate of liver cancer worldwide. In countries where curative options are available, however, early detection will lead to higher cure rates; people with known risks should undergo a screening protocol every six months.

It is more probable that a major decline in the incidence of the disease could be achieved by vaccinating everyone for hepatitis B and treating both hepatitis B and hepatitis C more effectively. In the future, we may also learn about the cause of liver cancer at a molecular level and develop better prevention and treatment strategies.

Part II

Hepatitis C Management and Liver Transplantation

13

An Overview of Hepatitis C Treatment

The primary objective of treatment for a hepatitis C infection is to completely eradicate the virus—in other words, for the person to have sustained clearance of the virus after the treatment is discontinued. For all practical purposes, the person is cured of hepatitis C infection at that stage. When people achieve sustained viral clearance (also known as sustained virological response, or SVR), they experience improvement in the inflammation of their liver and some improvement in the severity of scarring (fibrosis) and cirrhosis. Evidence also suggests that viral clearance is associated with no further progression of cirrhosis and a reduced incidence of liver cancer. However, even when people achieve viral clearance, they should still undergo surveillance for liver cancer if they have advanced fibrosis or cirrhosis.

> For people who have cirrhosis, sustained viral clearance of hepatitis C does not prevent development of liver cancer. It is important that they undergo regular surveillance for liver cancer throughout their lives or until there is liver biopsy evidence to suggest that the cirrhosis has reversed.

The field of treatment for hepatitis C is rapidly changing with the development of new medications. Until 2011, the standard medications to treat hepatitis C were a combination of

- Pegylated (long-acting) interferon *and*
- Ribavirin

In 2011, direct-acting antiviral medications (telaprevir and boceprevir) were approved by the FDA for use in combination with interferon and ribavirin, and these medications improved the rates of sustained viral clearance. More recently, new medications that can be used without interferon have been developed, and studies on these drugs report higher rates of sustained viral clearance for individuals who have chronic hepatitis C (table 13.1). Newer medications continue to be developed that show promise in treating hepatitis C infection.

The cure rates vary, depending on the presence of cirrhosis and previous treatment failure, as discussed in more detail in later chapters. As shown in figure 13.1, the current cure rates are nearly 90 percent for most people who have hepatitis C infection, and these rates improved by the end of 2014, when more interferon regimens became available for clinical use.

Interferon-free treatment (ledipasvir + sofosbuvir [Harvoni]) was approved for genotype 1 virus infections in October 2014. This oral treatment for two to six months has a cure rate of 95 percent for people who have the genotype 1 virus. The AbbVie regimen (Viekira Pak ± ribavirin) was approved in December 2014 (table 13.2), and this combination treatment will also give cure rates ranging from 95 to 99 percent with three to six months of treatment. The AbbVie regimen is also approved for people co-infected with hepatitis C and HIV and for people who have had a liver transplant. More importantly, the AbbVie regimen can be used for individuals who have renal failure.

Other oral treatment options may also become available in 2015. For all practical purposes, more than 95 percent of people—irrespective of previous treatment experience, presence of cirrhosis, race, or age—can expect to be cured.

Table 13.1. FDA-Approved Hepatitis C Medications, as of December 2014

Drug	*Administration*	*Duration of Treatment*	*Average Cure Rates*
Pegylated (long-acting) interferon and ribavirin:			
Pegasys or PegIntron	Once-a-week injection	12 months	Genotype 1: 50% Genotype 2: 80%
in combination with			
Ribavirin (Rebetol, Copegus)	By mouth	6 months	Genotype 3: 70%
Direct-acting antiviral drug (DAA) in combination with pegylated interferon and ribavirin:	DAA and ribavirin by mouth and interferon by injection		
Telaprevir (Incivek)	Three times a day	6 to 12 months	Genotype 1 only: 75%
Boceprevir (Victrelis)	Three times a day	6 to 12 months	Genotype 1 only: 69%
Simeprevir (Olysio)	Once a day	6 to 12 months	Genotype 1 only: 81%
Sofosbuvir (Sovaldi)	Once a day	3 months	Genotype 1: 90% Genotype 3: 94%
Direct-acting antiviral drug given with ribavirin:	Both drugs by mouth		
Sofosbuvir (Sovaldi)	Once a day	3 months for genotype 2;	Genotype 2: 90% to 95%
in combination with ribavirin	Twice a day	6 months for genotype 3	Genotype 3: 84%
Two direct-acting antiviral drugs:	One daily	3 months (can be used for 2 months	Genotype 1: ~95%
Ledipasvir and sofosbuvir combined in a single pill (Harvoni)		for those without cirrhosis and with low viral counts) 6 months for treatment-experienced individuals with cirrhosis	
Three-drug regimen containing paritaprevir/r, ombitasvir, and dasabuvir (Viekira Pak) with or without ribavirin	All oral	12 weeks for genotype 1b	99%
		12 weeks for genotype 1a without cirrhosis	97%
No ribavirin for genotype 1b without cirrhosis		24 weeks for genotype 1a with cirrhosis	95%
With ribavirin for genotype 1b with cirrhosis, genotype 1a with or without cirrhosis, and liver transplant recipients		24 weeks for liver transplant recipients	97%

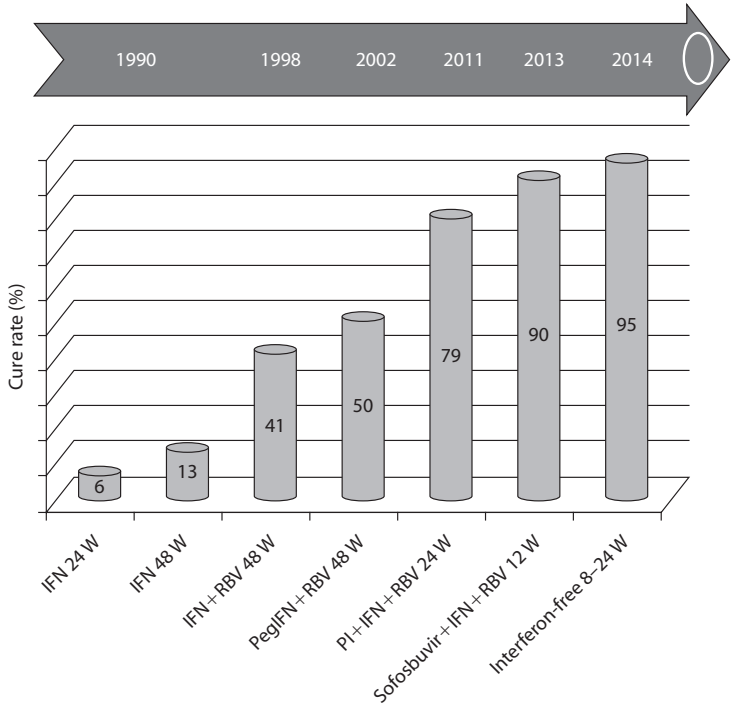


Figure 13.1. Percentage cure rates for infection with hepatitis C genotype 1 virus, 1990–2014 (IFN, interferon; RBV, ribovirin; pegIFN, pegylated interferon; PI, protease inhibitor; W, weeks of treatment)

Common Treatment Response Terminology

Individuals respond differently to treatment regimens, based on viral genotype, presence of cirrhosis, and previous exposure to treatment. When physicians discuss the treatment response of people who have hepatitis C, they often use the terminology shown in table 13.3.

If hepatitis C RNA is undetectable at week 12 (SVR12) or week 24 (SVR24) after treatment discontinuation, this can be considered as a cure. Rarely, a person's hepatitis C RNA levels may become detectable again, but this surge in RNA levels is often caused by reinfection. If hepatitis C RNA is undetectable at 12 weeks (SVR12) or 24 weeks (SVR24) after treatment discontinuation, it is not necessary to check hepatitis C RNA later. The hepatitis C antibody test result will remain positive for

Table 13.2. Interferon-Free, All-Oral Treatment Regimen for Hepatitis C Virus (HCV) Infection, as of December 2014

Treatment	*Cure Rates*
Ledipasvir and sofosbuvir as a single tablet (Harvoni) for 8 to 24 weeks (approved in October 2014)	12 weeks: 97% to 99% (94% for individuals who have cirrhosis) 8 weeks: 93% (without cirrhosis and with HCV RNA less than 6 million IU/ml) 24 weeks for treatment-experienced individuals with cirrhosis: 99% (based on small study)
AbbVie regimen for 12 to 24 weeks (paritaprevir/r [150/100 mg]–ombitasvir [25 mg] daily plus dasabuvir, 250 mg twice daily, [Viekira Pak], with or without ribavirin; this is a combination of four medications ± ribavirin) (approved in December 2014) *Note:* This regimen could be used for people with renal failure; not approved for advanced liver failure.	Genotype 1a without cirrhosis, 12 weeks with ribavirin: 97% Genotype 1a with cirrhosis, 24 weeks with ribavirin: 95% Genotype 1b without cirrhosis, 12 weeks without ribavirin: 99% Genotype 1b with cirrhosis, 12 weeks with ribavirin: 99% Liver transplant recipients, 24 weeks with ribavirin: 97% For those with HIV and hepatitis C: same as those without HIV

Table 13.3. Types of Responses during Hepatitis C Treatment and Their Meanings

Response	*Meaning*
Rapid viral response	Hepatitis C virus (HCV) RNA becomes undetectable at week 4 of treatment.
Early viral response	HCV RNA becomes undetectable or shows a 2-log decline compared with baseline at week 12 of treatment. Response could be either partial or complete. *Partial early viral response:* HCV RNA shows 2-log decline compared with baseline at week 12 of treatment but remains detectable. *Complete early viral response:* HCV RNA is undetectable at 12 weeks.
End-of-treatment response	Undetectable HCV RNA at the end of the recommended duration.
Sustained viral response (SVR)	Absence of HCV RNA at weeks 4 to 24 after treatment discontinuation. If HCV RNA is undetectable at 4 weeks after discontinuation, it is called SVR4; if undetectable at 12 weeks, SVR12; and if undetectable at 24 weeks, SVR24.

the rest of the individual's life and does not indicate the presence of active infection.

- If hepatitis C RNA is undetectable at 12 or 24 weeks (or later) after treatment discontinuation, this is considered a cure. There is no need for retesting.
- The hepatitis C antibody test will always remain positive and does not indicate the presence of ongoing hepatitis C infection.

Tests Done before Initiating Treatment

A few basic tests need to be done before starting treatment. In addition, physicians may perform some optional tests, depending on the treatment regimen, age of the patient, other health conditions, and previous treatment exposure (table 13.4).

Table 13.4. Tests Performed before Starting Treatment for Hepatitis C

Basic tests:
Hepatitis C RNA quantitative
Hepatitis C virus genotype
Liver function tests
Hemoglobin, white blood cells with differential, platelets
Thyroid-stimulating hormone
Blood tests for hepatitis A, hepatitis B, and HIV
Stress test (treadmill), electrocardiogram (for people 50 years or older and people with heart disease)
Ultrasound of liver
Optional additional tests:
Hemoglobin A1C (for people who have diabetes)
IL28B polymorphism (optional, to predict treatment response)
Tests for viral mutation
Liver biopsy or FibroScan (if not done before)

Table 13.5. Treatment Classifications for Hepatitis C Virus (HCV)

Treatment Classification	*Definition*
Treatment-naive	Individuals who have had no previous treatment for hepatitis C
Treatment relapsers	Individuals who clear the hepatitis C virus (HCV RNA negative) during treatment but become HCV RNA positive when treatment is discontinued
Null responders	People who have little response to treatment (usually less than 2-log decline in HCV RNA counts)
Partial responders	People who do not clear the virus during treatment but have more than 2-log decline in HCV RNA during treatment
Breakthrough nonresponders	Individuals whose HCV RNA levels become undetectable at some stage during treatment, but levels become detectable again while still receiving treatment
Nonresponders	Includes relapsers, breakthrough nonresponders, partial responders, and null responders
Treatment-intolerant	People who stopped treatment because of side effects

Assessment of Treatment Response

Individuals' response to treatment will depend on several factors, including whether they have responded to previous treatments. For example, if the person has never received any treatment (treatment-naive), that person is likely to respond better than someone who has not responded to previous treatment (treatment nonresponder or treatment relapser). Physicians may use various terms to discuss an individual's treatment status (table 13.5).

Treatment Limitations

The improvement in treatment options has made hepatitis C more easily curable with 8 to 24 weeks of treatment. The major limitation is access to treatment because of the costs. The hepatitis C treatment costs

around $100,000 per person. If an individual is cured of hepatitis C, however, future costs, including the cost of liver transplantation, will be reduced, and that person will have an improved life expectancy. The exorbitant costs of treatment may reduce access to treatment for many people, even in high-income countries. The competition in this field may help to reduce future costs of these medications and may lead to global eradication of hepatitis C.

14

Treatment with Interferons and Ribavirin

Interferons are complex proteins made by the immune system in response to infection by viruses and bacteria. They have many properties, including the ability to influence inflammation, eradicate viruses, and scar the liver. There are different types of interferons; alpha-interferon is the type used to treat hepatitis C.

Ribavirin is a synthetic nucleoside analogue that acts against hepatitis C. Although its exact mechanism of action remains unknown, researchers have suggested that it inhibits viral-dependent RNA enzymes. Ribavirin alone does not have significant antiviral effects against hepatitis C, so it is always used in combination with other medications.

History of Treatment with Interferons and Ribavirin

In the past, hepatitis C was treated with standard interferon, which had to be injected under the skin three times a week. The cure rates were low—approximately 6 percent when individuals were treated with standard interferon alone for 6 months, and approximately 12 percent when treated for 12 months for the genotype 1 virus. Later, ribavirin was added to standard interferon for hepatitis C treatment, and cure rates increased up to 40 percent with 12 months of treatment for genotype 1. Currently, standard interferon is rarely used except in a few low-income countries.

In 2002, pegylated interferon (a long-acting injection given once a week under the skin) was introduced. Pegylated interferons are made by adding a polyethyleneglycol (PEG) molecule (a water-soluble, nontoxic

polymer) to standard interferon, resulting in a larger drug molecule with longer antiviral activity in the body and slower clearance from the body. Thus, pegylated interferons need to be given only once a week, as opposed to three times a week for standard interferon. Treatment for 12 months with pegylated interferons and ribavirin together was found to cure between 42 and 54 percent of individuals who had the genotype 1 virus. For genotypes 2 and 3, 24 weeks of treatment with pegylated interferon and ribavirin cured 80 percent and 60 to 70 percent of individuals, respectively.

Until 2011, the standard treatment for hepatitis C infection was a combination of pegylated interferon injected once a week and ribavirin 800 to 1,200 mg given by mouth daily (in two daily divided doses).

Treatment Response with Pegylated Interferon and Ribavirin

A person's response to treatment with pegylated interferon and ribavirin depends on many factors, including:

- Genotype of the virus
- Viral counts
- Presence of cirrhosis
- Response pattern to previous treatment
- Ability to tolerate a full dose of ribavirin
- Presence of the IL28B (human) genetic mutation
- Race

Of the above factors, the relevance of IL28B polymorphism to treatment response was identified in a genomewide association study. A single nucleotide change in an individual's IL28B gene (located on human chromosome 19) predicted the likelihood of response to interferon-based treatment: individuals with C/C had a better response than those with C/T or T/T polymorphism. Less than one-third of the U.S. population has the CC polymorphism, but it is more common among people of Asian ethnicity. Now that other, more effective antiviral drug regimens are

available, this genetic mutation and its effect on treatment response have become less relevant.

Table 14.1 lists factors that predict a poor response to combination treatment with pegylated interferon and ribavirin. Of these factors, viral genotype is the most important in predicting response. Genotype 1 is the most common hepatitis C genotype in the United States, occurring in approximately 70 percent of people who have hepatitis C. The treatment response rate in people with genotype 1 is lower than in those with genotypes 2 and 3; people with genotypes 4, 5, and 6 also have lower treatment responses. Table 14.2 lists the average cure rates according to genotype, as reported in large clinical trials studying treatment with pegylated interferon and ribavirin.

Genotype also affects the duration of treatment with interferon and ribavirin. Until 2011, the optimal treatment of hepatitis C for genotypes 1, 4, 5, and 6 included pegylated interferon and a dose of ribavirin based on the individual's weight (a dose of 800 to 1,200 mg daily) for 12 months.

Table 14.1 Factors That Predict Poor Response to Pegylated Interferon and Ribavirin

Viral factors:
Genotype 1
High viral counts
Host factors:
IL28B polymorphism—C/T, T/T
Old age
Male sex
African American race
Presence of cirrhosis
Co-infection with HIV
Obesity
Diabetes
Increase in liver iron
Treatment factors:
Absence of rapid viral response
Incomplete viral response
Social factors:
Lack of adherence to treatment
Continued substance abuse
Uncontrolled mental health issues

Table 14.2. How Hepatitis C Virus Genotype Affects Cure Rates with Pegylated Interferon and Ribavirin

Virus Genotype	*Average Cure Rates*
Genotype 1 (overall):	
Individuals with mild to moderate fibrosis	45% to 55%
Individuals with advanced fibrosis or cirrhosis	30% to 40%
African American individuals	30% to 40%
Genotype 2	75% to 85%
Genotype 3	60% to 70%
Genotype 4	~60%

Table 14.3. Duration of Treatment and Dose of Ribavirin (when used with interferons)

Virus Genotype	*Ribavirin Dose*	*Duration*
Genotype 1	Individual's weight less than 75 kg: 1,000 mg daily Individual's weight more than 75 kg: 1,200 mg daily	12 months
Genotype 2 or 3	800 mg daily	6 months
Other genotypes	Insufficient data; perhaps same as genotype 1	Insufficient data; perhaps 12 months

For individuals with genotypes 2 or 3, the treatment duration was 6 months and the ribavirin dose was fixed at 800 mg daily (table 14.3). The interferon dose is usually fixed for peginterferon alfa-2a (Pegasys) and is weight-based for peginterferon alfa-2b (PegIntron).

Studies showed that the type of pegylated interferon (PegIntron or Pegasys) did not have any influence on cure rates. The response rates were higher when the pretreatment viral loads were lower (less than 600,000 IU/ml versus more than 600,000 IU/ml) and when there was less scarring of the liver (cirrhosis versus no cirrhosis). (Note that viral loads are often expressed as log values [exponents of 10], which converts large numbers to small numbers—for example, 3 log is $10 \times 10 \times 10$, or 1,000; 1-log reduction in viral load means a 90 percent reduction,

and 2-log reduction means 99 percent reduction.) African Americans had 10 to 15 percent lower response rates than whites. Response rates of Hispanics were in between those of Caucasians and African Americans.

Precautions before Starting Treatment

Treatment with interferon is not advised for people who have certain conditions, such as decompensated cirrhosis (that is, a worsening of cirrhosis), a history of untreated major depression, or untreated hypothyroidism, because these conditions could worsen with interferon treatment. Table 14.4 lists all the conditions that would make interferon treatment inadvisable.

Ribavirin is a drug that causes birth defects in children and should not be used by men or women planning to have children and for six months after childbirth.

> Warning: Ribavirin is likely to cause serious birth defects. Women and men should not take ribavirin if they are planning to get pregnant / have children, if they or their partners are currently pregnant, or for six months after childbirth.

Ribavirin should be used with caution for people who have anemia and heart disease. For individuals who have kidney disease, the dose of ribavirin needs to be modified because the drug is eliminated through the kidneys. Kidney function is measured as serum creatinine level or

Table 14.4. Who Should Not Take Interferon-Based Treatments?

Individuals who have:
History of decompensated cirrhosis
History of untreated major depression
Neutrophil cell count less than 1,000/ml
Platelet count less than 40,000/ml
Untreated hypothyroidism
Convincing evidence of an autoimmune disease (for example, lupus)
Sarcoidosis
History of serious intolerance to interferons

Table 14.5. Treatment Guidelines for Ribavirin and Interferon

Creatinine Clearance	*Dose of Ribavirin*	*Dose of Pegasys or PegIntron*
30 to 50 ml/min	Alternating doses, 200 mg and 400 mg every other day	Pegasys: 180 micrograms weekly (full dose) PegIntron: reduce dose by 25%
Less than 30 ml/min	200 mg daily	Pegasys: 135 micrograms weekly PegIntron: reduce dose by 50%
Hemodialysis	200 mg daily	Pegasys: 135 micrograms weekly PegIntron: reduce dose by 50%

creatinine clearance; when serum creatinine increases, creatinine clearance decreases. If creatinine clearance is less than 50 ml/minute, the ribavirin dose needs to be adjusted as shown in table 14.5. The table lists the dose information for ribavirin and interferon for individuals who have decreased kidney function. If significant side effects or laboratory abnormalities appear with this dosing, ribavirin should be discontinued.

Monitoring during Treatment

Individuals who start treatment should be under the care of an experienced physician and should follow up regularly with their physician. Before starting treatment, it is extremely important for both the individual who starts treatment and the immediate family members to learn about the treatment protocol and the potential side effects. A well-informed individual is more likely to complete treatment and have a successful outcome. It is also extremely important for individuals to ask questions of the physician until they thoroughly understand the treatment protocol. The physician should be contacted immediately if there are unexpected side effects.

As described in chapter 13, the physician will perform a number of blood tests before initiating treatment. During the course of treatment, the physician will continue to monitor blood tests to identify and treat potential side effects (table 14.6).

To ensure the best response to treatment, individuals should take the medications as directed during the first three months. Similarly, physi-

Table 14.6. Timeline and Tests for Monitoring Treatment Response

Time	*Tests*
2, 4, 6, 8 weeks after starting treatment (more frequently if necessary)	Liver function tests Hemoglobin, white blood cells with absolute neutrophil counts, platelets
3 months	Liver function tests Hemoglobin, white blood cells with neutrophil counts, platelets Thyroid-stimulating hormone Hepatitis C virus (HCV) RNA levels: *If minimal or no change in HCV RNA, stop treatment.* If significant decrease (more than 2-log decrease in HCV RNA; intermediate response), continue treatment until 6 months and assess HCV RNA levels again at 6 months.
6 months	Liver function tests Hemoglobin, white blood cells with neutrophil counts, platelets Thyroid-stimulating hormone HCV RNA levels Genotypes 2 and 3: discontinue treatment For all other genotypes, continue treatment until 12 months if HCV RNA is negative at 6 months. If HCV RNA is positive at 6 months, treatment should be discontinued since it is futile to continue.
9 and 12 months, and posttreatment 3 and 6 months	Liver function tests Hemoglobin, white blood cells with neutrophil counts, platelets Thyroid-stimulating hormone HCV RNA levels

If HCV RNA is undetectable at 3 to 6 months after discontinuation of treatment, this is considered to be sustained viral clearance (a cure, for all practical purposes). Additional tests include a questionnaire for depression and eye tests if there are visual problems.

cians will try not to reduce the dose in the first three months, so as to obtain the best results.

At three months, people who do not show a significant reduction in viral amount (viral clearance or 2-log [99 percent] reduction in viral amount) are unlikely to have a sustained viral clearance, and physicians

will discontinue treatment at that time. Because genotypes 2 and 3 show an overall treatment response rate of nearly 70 to 80 percent, physicians may not need to monitor viral response at three months and may choose to continue treatment for six months.

Treatment of Relapsers, Partial Responders, or Nonresponders

- Relapsers are individuals who respond to treatment and have undetectable hepatitis C RNA levels during and at the end of treatment, but when treatment stops, their hepatitis C RNA levels become detectable.
- Partial responders are individuals who have some response, but hepatitis C RNA never becomes undetectable during treatment.
- Null responders are individuals who show very little response to treatment (usually less than 2-log decline in hepatitis C RNA counts in the first 12 weeks).

Previously, these groups of people were re-treated with pegylated interferon and ribavirin. Now that direct-acting antiviral alternatives are available, relapsers and nonresponders are not likely to be offered retreatment with pegylated interferon and ribavirin.

Side Effects

Interferon Treatment

Side effects associated with interferon are a major limitation to treatment using this drug. The severity of the side effects can range from mild to severe and, rarely, can be life-threatening.

Before starting treatment with interferon or ribavirin, people should understand all the potential side effects and their potential severity, how these side effects will affect their lives, and how they may be partly or completely controlled with either medications or minimal lifestyle changes. In addition, people should understand how they will be monitored for those side effects and any potential complications and what to

do if serious side effects occur. The challenge for both patient and physician is to continue both medications despite the side effects, without reducing the dose or missing doses, for the entire duration of the treatment, which can range from 6 to 12 months. People who take the medications without reducing or missing doses have a better cure rate.

The potential side effects of interferon are listed and described in table 14.7. The most common side effect associated with interferon is flulike symptoms, which usually disappear after two to four weeks. Serious side effects are very rare (they occur in less than 2 percent of individuals undergoing interferon treatment). These side effects include autoimmune diseases (such as thyroid disorders), seizures, severe depression, cardiac failure, visual problems (retinopathy), interstitial fibrosis, infections (sepsis), and kidney failure. Although many of these

Table 14.7. Side Effects of Interferon

Common side effects:
Flulike symptoms (headache, fever, body ache)
Fatigue
Irritability
Depression
Sleep disturbances
Dry mouth
Dry cough
Redness at the injection site
Rare side effects:
Weight loss (10 to 12 lbs. usually)
Mouth ulcers
Diarrhea
Hair loss
Seizures
Visual problems
Interstitial fibrosis (inflammation of lung tissue)
Bone marrow suppression (low white blood cells, low platelets, anemia)
Thyroid function abnormalities
Infections
Kidney failure
Serious depression
Psychosis
Infections at the injection site

are likely to reverse when treatment is stopped, autoimmune diseases may persist.

Ribavirin Treatment

The most common and serious side effect of ribavirin is hemolytic anemia, in which the red blood cells break down. Approximately 10 percent of people taking ribavirin experience a decrease in hemoglobin to less than 10 g/dl, and this is five times more common in women. Approximately half of people taking combination interferon and ribavirin treatment experience a decrease in hemoglobin of 3 g/dl or more. Hemolytic anemia is readily reversible, but caution must be exercised for people who are anemic or have significant heart disease or kidney failure.

Ribavirin can cause serious birth defects in fetuses, and for that reason, people who take ribavirin should not be pregnant or be considering pregnancy. Both men and women who take ribavirin should use contraception during treatment and for six months after treatment. If pregnancy occurs during treatment or within six months after treatment, individuals should immediately consult their physician.

Combination Treatment with Interferon and Ribavirin

The combination treatment of interferon and ribavirin appears to cause more nausea, anorexia, shortness of breath, skin rash, itching (pruritus), and sleep disturbances than interferon alone. Anemia is also more common with the combination treatment than with interferon alone.

Management of Side Effects

Drinking plenty of water and eating properly are important during interferon treatment. Regular exercise may also help to reduce some of the symptoms. A positive attitude is essential; these symptoms will improve with time.

Flulike Symptoms

Symptoms of fatigue, fever, headache, tremors, and body aches are reported in up to two-thirds of people undergoing treatment. Usually, these

symptoms occur soon after the injection and last between 24 and 72 hours. The symptoms typically continue to improve after the first four to six weeks as the body gets used to the medication. The first injection may be the most difficult if the person is not prepared for the fever (often high), headache, and body aches (myalgia).

To reduce the effect of these symptoms, the person can take the injection before going to bed at night and can take either acetaminophen (Tylenol 500 mg) or ibuprofen (Motrin or Advil 400 to 800 mg) 20 to 30 minutes before the injection and, if necessary, 6 to 8 hours later. Theoretically, because of possible liver damage caused by acetaminophen, ibuprofen may be the better choice, but there have been no comparative studies. People who have cirrhosis, bleeding, or kidney damage (elevated creatinine) should not take ibuprofen or any other nonsteroidal anti-inflammatory drugs.

If headache or body aches (myalgia) are the primary symptom, the individual should seek help from the treating physician, who may prescribe a variety of medications, including those used for migraine (propranolol or sumatriptan [Imitrex]) and, rarely, drugs for myalgia (gabapentin).

Irritability, Insomnia, and Depression

Collectively called the "neuropsychiatric" complications of interferon, irritability, insomnia, and depression occur in approximately 20 percent of people undergoing treatment. In general, people who have a history of depressive illness seem to be more likely to develop these symptoms than individuals who do not have this history.

As many as 50 percent of people undergoing this treatment have difficulty sleeping. Having good sleep habits, including going to bed at the same time every night, not watching television or using electronics before going to sleep, and not having stimulants such as coffee or tea before going to bed, may help some people sleep better. Over-the-counter medications such as antihistamines (diphenhydramine [Benadryl] 25 to 50 mg) or melatonin may also help a few people. People who have underlying depression may find that their insomnia improves when their depression is adequately controlled. People with insomnia and depression

may want to ask their physician about using a selective serotonin reuptake inhibitor with sedative action. People who have insomnia without any depressive symptoms could ask their physician about prescription sleep aids, such as zolpidem (Ambien) 5 to 10 mg, trazodone (Oleptro), or temazepam (Restoril) 15 to 30 mg.

Depression may be more common in people who have hepatitis C infection than in those who do not. The higher incidence of depression may be partly due to anxiety about the diagnosis and its long-term effect on life expectancy. Unfortunately, the underlying psychiatric problems can affect interferon-based treatment, because a significant number of people either do not continue with the treatment as directed or do not seek treatment. In addition, a few physicians are reluctant to treat a hepatitis C infection in people who already have psychiatric symptoms. However, there is evidence that these people could be treated effectively in a multidisciplinary setting with a psychiatrist, supportive nursing staff, and a liver specialist (hepatologist) (table 14.8).

Because neuropsychiatric symptoms do not improve with time and may get worse during treatment, individuals who experience these symptoms should seek medical help and receive appropriate treatment. These symptoms occur because of chemical imbalances (in the serotonin, opioid-dopamine, norepinephrine systems) caused by interferon and will improve after the completion of treatment. Usually, these symptoms can improve with small doses of antidepressants. The common medications

Table 14.8. Management of Neuropsychiatric Symptoms in Treating People Who Have Hepatitis C

Treatment with interferon is not recommended for people who have untreated serious psychiatric illness or had previous suicide attempts.
Before starting treatment with interferon, people should have their depression controlled.
An antidepressant, such as a selective serotonin reuptake inhibitor, may be the first drug given to treat depression, and most people require only small doses.
Having a team of medical professionals, including a psychiatrist, hepatologist, and support staff, is crucial to successful management and treatment for people who have hepatitis C and neuropsychiatric symptoms.

used to treat interferon-related depression include citalopram (Celexa) and paroxetine (Paxil), although any selective serotonin reuptake inhibitor could be used for this purpose. The physician may choose these drugs based on the person's other symptoms. For example, paroxetine may help people who suffer from insomnia. Sometimes physicians have to find a suitable drug by trial and error. People may need to wait three to six weeks before seeing any improvement.

Dry Mouth

About 10 percent of people undergoing interferon treatment experience dry mouth, which can be a serious side effect. People could try to alleviate the dryness by sucking on hard candy or mints, ice cubes, or popsicles, or by using lemon glycerin swabs or artificial saliva sprays, swabs, or solutions.

Dry Cough

Approximately 10 to 20 percent of people taking interferon have a dry cough (a cough that does not bring up any mucus). Over-the-counter medications such as guaifenesin, as well as cough suppressants such as benzonatate, may be helpful. If the physician confirms that there is no chest infection, treatment can be continued without any short-term or long-term effects.

Hair Loss

Up to one-third of people taking interferon experience hair loss and hair thinning. For most people, this hair loss need not be worrisome because hair growth returns when the treatment is discontinued. People who are sensitive to hair loss can reduce both hair loss and hair breakage by avoiding coloring, perming, or other chemical hair treatments, putting the hair in ponytails or buns, or other habits that may cause hair to break. Keeping a short hairstyle may help make this side effect less noticeable.

Skin Complications

Redness at the injection site is common and usually very mild. This reaction can be minimized by injecting the medication at different places

on the body. Although the reactions may vary with the type of pegylated interferon, there is no convincing evidence to support switching from one preparation to another because of mild reaction at the injection site. Infections at the injection site are extremely rare and are often caused by poor skin cleansing before injection.

Skin rashes are very common in people taking combination interferon and ribavirin treatment. Up to one-third of people experience rashes (dry skin, discrete itchy areas, or generalized rash that is very itchy) due to ribavirin. Using moisturizing soaps and lotions, such as Aveeno, petroleum jelly, Eucerin, or Lac-Hydrin, may be helpful for many people who have dry skin. Ribavirin rashes may start in the lower extremities and spread upward. The physician may reduce the dose of ribavirin, prescribe a topical steroid cream, or suggest another topical preparation to help alleviate these symptoms. A compounded mixture of 0.5 percent menthol with 0.1 percent triamcinolone ointment applied twice daily on the affected area has helped some individuals.

Mouth Ulcers

Mouth ulcers are an infrequent symptom. People have tried to provide temporary relief using over-the-counter benzocaine gels or pastes to cover the ulceration. Also, some temporary relief may be achieved with "magic mouthwash," which is a mixture of medications in syrup form that usually consists of an antihistamine, an antacid, and an anesthetic (lidocaine), as well as other medications including an antibiotic to kill bacteria. The physician can write a prescription for the medications needed for the mouthwash, according to the person's needs.

Visual Problems

Visual problems are extremely rare (perhaps less than 1 in 100,000), but they require immediate help and discontinuation of interferon treatment. Inflammation of the optic nerve (optic neuritis) may cause visual disturbances and is diagnosed by an eye examination.

Anemia

Anemia is a common side effect of ribavirin therapy. It is caused by ribavirin breaking down red blood cells (hemolysis) and, to a lesser extent, by interferon causing bone marrow suppression.

Although people are usually diagnosed with anemia after routine blood tests during treatment, some people may experience extreme fatigue or shortness of breath because of a sudden decline in hemoglobin. Currently, there are no treatments to prevent red blood cells from breaking down, but studies are in progress to find alternatives to ribavirin or to modify the drug to prevent this complication.

It is important to have blood tests, including tests for hemoglobin (or hematocrit), platelets, and white blood cells, before treatment and then regularly throughout treatment to monitor treatment response and any possible harmful side effects (table 14.9).

Hemoglobin should be checked every two weeks for the first eight weeks. Usually, the decline in hemoglobin stabilizes by four to eight weeks. After that, hemoglobin needs to be checked only every four to six weeks. For people who have rapidly declining hemoglobin or borderline hemoglobin levels, more frequent follow-up is important. People aged 50 years or older and those who have a history of coronary artery disease should have electrocardiogram tests before starting treatment because a rapid decline in hemoglobin may precipitate a heart attack.

Usually, hemoglobin can decline by 2 to 4 g/dl during treatment. To improve a person's hemoglobin levels, a physician will use guidelines to assess whether the dose of ribavirin and interferon needs to be changed based on the individual's hemoglobin levels, but also based on the person's medical history, symptoms, and other illnesses. Studies have shown

Table 14.9. Common Blood Test Abnormalities during Treatment for Hepatitis C

Decrease in hemoglobin (ribavirin and, to some extent, interferon)
Decrease in white blood cells (interferon)
Decrease in platelets (interferon)
Abnormalities in thyroid tests (interferon)

that the chances of a cure (sustained viral clearance) decrease with a reduction in ribavirin dose. Therefore, a physician needs to perform a careful balancing act between clearing the virus without causing serious harm.

Although reducing the dose of ribavirin improves hemoglobin levels, to optimize the treatment for hepatitis C, other medications—such as growth factor—that promote red cell production are increasingly being used to avoid the need for ribavirin dose reduction. Erythropoietin (Procrit, Epogen, Aranesp) is a commercially available growth factor that promotes red blood cell production. These drugs are approved for use by people with anemia who also have kidney failure or cancer. Most insurance companies have also approved the use of erythropoietin for ribavirin-associated anemia.

The ribavirin dose needs to be adjusted when hemoglobin decreases, as shown in table 14.10, particularly for people who have heart disease, because, as noted above, anemia may precipitate a heart attack (myocardial infarction).

The physician may prescribe erythropoietin for people who have a hemoglobin level of less than 12 g/dl before treatment or for those who had normal hemoglobin before treatment but the level decreases to less than 10.5 g/dl. The dose of erythropoietin may be increased or decreased depending on the person's response. The usual dose of Procrit or Epogen

Table 14.10. Recommendations for Ribavirin Dose Reduction

Condition	*Hemoglobin Level*	*Ribavirin Dose*
No heart disease	10 g/dl or more	Full dose
	8.5 g/dl to 10 g/dl	Reduce dose to 600 mg/day
	Less than 8.5 g/dl	Discontinue treatment
History of heart disease	More than 2 g/dl decrease during any 4-week period during treatment	Reduce dose to 600 mg/day
	Less than 8.5 g/dl or less than 12 g/dl after 4 weeks of dose reduction	Discontinue ribavirin

is 40,000 to 60,000 units injected once a week. If an individual is also iron-deficient, erythropoietin will not be effective in increasing red blood cells, so the person should take iron supplements to replenish iron stores (ferrous sulfate 325 mg three times daily) before starting erythropoietin.

If hemoglobin decreases to less than 9 g/dl despite the use of iron supplements and erythropoietin, the individual's dose of ribavirin should be reduced by half. If the hemoglobin level then improves, the ribavirin can be gradually increased again to reach the optimal dose. On the contrary, if the person's hemoglobin continues to decrease despite all these efforts, the medications should be permanently stopped.

Although hemoglobin decrease is primarily caused by ribavirin, interferon, as noted above, may also play a minor role because it causes bone marrow suppression.

Decrease in White Blood Cells

There are predominantly two types of white blood cells: neutrophils and lymphocytes. Interferon causes a decline in neutrophils (a condition called neutropenia), and very low neutrophil level may make a person prone to bacterial infections. The physician will periodically measure neutrophil counts to ensure that they remain at about 500/microliter (a microliter is one-thousandth of a milliliter). Although neutropenia is common during interferon treatment, this condition is critical only if absolute neutrophil counts are less than 500 (normal range, 1,500 to 8,000/microliter). If the absolute counts become critical, there are two options. The physician can reduce the dose of interferon (table 14.11), which does not reduce the antiviral effects as much as reducing the dose of ribavirin, or can prescribe another growth factor (a granulocyte cell stimulating factor, such as Neupogen) for white cells. This treatment, just as with erythropoietin, is expensive and has to be done under careful guidance and follow-up. The physician may start Neupogen at a dose of 300 micrograms injected weekly and then increase the dose up to three times a week, based on the person's response to therapy. The physician and treating team will perform laboratory tests about

Table 14.11. Treatment Guidelines for Interferon

Cell Count (per microliter)	*Interferon Dose Reduction*
Absolute neutrophil count:	
Less than 750	PegIntron: reduce dose by half Pegasys: reduce to 135 micrograms
Less than 500	PegIntron: discontinue Pegasys: discontinue and restart at 90 micrograms when absolute neutrophil count is more than 1,000
Platelet count:	
More than 80,000	No dose reduction
50 to 80,000	PegIntron: reduce by half Pegasys: no change
25 to 50,000	PegIntron: discontinue Pegasys: reduce by half
Less than 25,000	Stop interferon

48 hours after the growth factor injection to check the person's response to therapy, because if the tests are done too soon, the result may be falsely elevated.

Thyroid Function Abnormalities

During treatment, abnormalities in thyroid function can arise. An underfunctioning thyroid (hypothyroidism) is more common than an overfunctioning thyroid (hyperthyroidism). If the thyroid-stimulating hormone level is high, the thyroid is underfunctioning (the pituitary gland is producing more thyroid-stimulating hormone to stimulate the thyroid gland). In hyperthyroidism, the thyroid-stimulating hormone level is low. Both conditions can be treated easily. People who have high thyroid-stimulating hormone are treated with thyroid hormones (such as levothyroxine [Synthroid]); this treatment is not associated with any side effects. People who have low thyroid-stimulating hormone require treatment through a specialist in endocrine diseases, who probably will use medications, or radioactive iodine in some circumstances. Although thyroid abnormalities may be temporary in most people, occasionally they can be permanent.

Other Uncommon Complications

Some people develop fluid around the heart (pericardial effusion) or diabetes while taking interferon. Serious depression, psychosis, or suicidal thoughts during treatment, although rare, are considered an indication for immediate discontinuation of treatment. These people should seek immediate help from a psychiatrist.

For more than two decades, interferon was the backbone of hepatitis C treatment. However, it was associated with significant side effects, which resulted in poor adherence, drug discontinuation, and treatment failure. Moreover, many people were unwilling to seek treatment because they wanted to avoid the potential and serious side effects. Future treatment of hepatitis C may not involve the use of interferon, given the serious side effects associated with such treatments and the availability of better treatment options. Although it was initially thought that ribavirin might not be used in interferon-free regimens, it seems that some groups of patients (those with cirrhosis, previous treatment failure, or certain genotypes) may continue to benefit from the addition of ribavirin to their direct-acting antiviral medication regimen.

15

Interferon in Combination with Direct-Acting Antiviral Drugs

Until 2011, hepatitis C was treated with a combination of pegylated interferon and ribavirin. In 2011, the U.S. Food and Drug Administration approved two direct-acting antiviral drugs (first-generation protease inhibitors, boceprevir [Victrelis] and telaprevir [Incivek]) to be used in combination with pegylated interferon and ribavirin to treat individuals who have hepatitis C genotype 1 infection. These medications improved the rates of sustained viral clearance. In late 2013, two additional direct-acting antiviral drugs (a second-generation protease inhibitor, simeprevir [Olysio], and an NS5B nucleotide inhibitor, sofosbuvir [Sovaldi]) were approved; studies have shown these to have high rates of sustained viral clearance. In October 2014, ledipasvir (an NS5A inhibitor) in combination with sofosbuvir (the combination called Harvoni) was approved for treatment of genotype 1 infection, and in November 2014, simeprevir (Olysio) in combination with sofosbuvir (Sovaldi) was approved for genotype 1 infection. In December 2014, AbbVie's three-drug regimen (Viekira Pak) containing paritaprevir/r (protease inhibitor with ritonavir), ombitasvir (an NS5A inhibitor), and dasabuvir (an NS5B non-nucleoside inhibitor), with or without ribavirin, was approved for treating people with genotype 1 infection, including those co-infected with HIV and hepatitis C and those who have had a liver transplant.

This chapter provides a brief overview of direct-acting antiviral medications and their success rates and side effects, in combination with interferon and ribavirin, for treating chronic hepatitis C.

Direct-Acting Antiviral Drugs

Progress in understanding the life cycle of the hepatitis C virus helped scientists to develop drugs that can inhibit hepatitis C viral replication at various stages of the virus's life cycle and to learn about potential drug resistance. Because each medication has a different target, the drugs have varying potency, efficacy against different viral genotypes, and drug resistance profiles.

The hepatitis C virus is an RNA virus composed of structural and nonstructural proteins. Most drugs developed thus far have been targeted toward inhibiting three groups of hepatitis C nonstructural proteins: NS3-4A proteases, NS5A proteins, and NS5B polymerases.

The NS3-4A proteases are an essential component of viral replication. Inhibiting these proteases blocks replication; hence, the drugs are known as protease inhibitors. The FDA has approved three protease inhibitors—telaprevir, boceprevir, and simeprevir—and many more are in various stages of development; paritaprevir/r was approved as part of the AbbVie regimen (Viekira Pak).

NS5A is a membrane-associated protein that also plays an important role in hepatitis C viral replication. In October 2014, one of the NS5A inhibitors, ledipasvir (developed by Gilead Sciences), was approved by the FDA to be used in combination with sofosbuvir as a single pill (Harvoni), and in December 2014, ombitasvir was approved by the FDA as part of the AbbVie regimen (Viekira Pak). Several drugs that inhibit NS5A are in the advanced stages of development, including daclatasvir (developed by Bristol-Myers Squibb) and are likely to be approved in 2015.

NS5B polymerase is an important enzyme responsible for the synthesis of hepatitis C RNA. Two types of NS5B polymerase inhibitors, nucleoside/nucleotide polymerase inhibitors and non-nucleoside polymerase inhibitors, are being developed to treat hepatitis C infection. In December 2013, the FDA approved the NS5B nucleotide inhibitor sofosbuvir, which can be used in combination with interferon and ribavirin for viral genotypes 1 and 4, and in combination with ribavirin (without interferon) for viral genotypes 2 and 3. Sofosbuvir is one of the most important advances in the treatment of hepatitis C infection because of its high

Table 15.1. Direct-Acting Antiviral Drugs by Class, Potency, Genotype Coverage, and Resistance

Class of Drug	*Potency*	*Genotype Coverage*	*Possibility of Resistance*
Protease inhibitors	High	Genotype-specific	High risk
NS5A inhibitors	High	Variable	Moderate risk
NS5B nucleoside/ nucleotide inhibitor	Intermediate	All genotypes	Very low risk
NS5B non-nucleoside inhibitor	Intermediate	Genotype-specific	High risk

Note: Protease inhibitors and NS5A inhibitors with coverage of all genotypes are in different stages of development. Currently available NS5A inhibitors have some activity against all genotypes but are more effective against genotype 1.

efficacy and high barrier to drug resistance. The NS5B non-nucleoside inhibitor dasabuvir (developed by AbbVie as part of Viekira Pak) was approved in December 2014, and many others are in advanced stages of development.

The four categories of direct-acting antiviral drugs have different potencies, genotype coverage (all genotypes versus specific genotypes), and resistance potential (the possibility of the virus developing resistance to a particular drug), as listed in table 15.1. They also have different cure rates, side effects, and drug interactions with other commonly used drugs. Within each specific category of direct-acting antiviral drug there are varying properties, including genotype coverage.

Table 15.2 shows the direct-acting antiviral drugs that have been approved or are likely to be approved by the FDA. Of these drugs, only sofosbuvir is approved for use without interferon for people who have viral genotypes 2 and 3.

Of the drugs listed in table 15.2, only telaprevir (Incivek), boceprevir (Victrelis), simeprevir (Olysio), and sofosbuvir (Sovaldi) have been approved by the FDA in combination with interferon and ribavirin. All drugs except sofosbuvir are approved for only genotype 1. Only Viekira Pak is approved for transplant recipients and for individuals who have kidney failure. Both sofosbuvir and Viekira Pak are approved for people who also have HIV.

Table 15.2. Status of Approval of Direct-Acting Antiviral Drugs by the Food and Drug Administration, as of 2014–15

Class of Drug	*Drug Name*	*Virus Genotype*	*Approval Status*
Protease inhibitors	Telaprevir (Incivek)	Genotype 1	Approved
	Boceprevir (Victrelis)	Genotype 1	Approved
	Simeprevir (Olysio)	Genotype 1	Approved
	Paritaprevir-ritonavir	Genotype 1	Approved
NS5A inhibitors	Ledipasvir	Genotype 1	Approved
	Daclatasvir	All genotypes	Approved
	Ombitasvir	Genotype 1	Approved
NS5B nucleotide inhibitor	Sofosbuvir (Sovaldi)	All genotypes	Approved
NS5B non-nucleoside inhibitor	Dasabuvir	Genotype 1	Approved

Many other drugs are in various stages of trials, and the list is constantly changing (table 15.3). If many of these drugs continue to show promise in trials, they may be approved by the FDA and will increase the options available for treatment and possibly reduce the cost of hepatitis C treatment.

In general, compared with treatment with interferon and ribavirin alone, adding a direct-acting antiviral drug to the combined treatment regimen improves cure rates. The following sections cover the current treatment options with direct-acting antiviral drugs in combination with pegylated interferon and ribavirin. The use of these drugs without interferon is discussed in chapter 16.

Interferon and Ribavirin Combined with Protease Inhibitors

Adding a protease inhibitor to the combined treatment regimen of pegylated interferon and ribavirin was found to improve cure rates as follows:

- Rates improved by 30 percent for people who had mild to moderate fibrosis.
- Rates improved by 15 percent for people who had cirrhosis; studies included only a small proportion of people who had cirrhosis, so the true cure rate for individuals with cirrhosis remains to be assessed by further studies.
- An approximately 80 percent cure rate occurred for individuals who had disease relapse after previous treatments.

However, people who showed a partial or no response to previous treatment with pegylated interferon and ribavirin had relatively low cure rates when re-treated with a regimen that also included a protease inhibitor.

Currently, three protease inhibitors—telaprevir, boceprevir, and simeprevir—are approved by the FDA to treat individuals who have genotype 1 infection. These drugs have to be used in combination with

Table 15.3. Other Direct-Acting Antiviral Drugs (with manufacturers) in Various Stages of Development

Protease inhibitors (second-generation):
Danoprevir (Roche)
Vaniprevir (Merck)
Grazoprevir (Merck)
Vedroprevir (Gilead)
Sovaprevir (Achillion)
NS5A inhibitors:
Velpatasvir (Gilead)*
PPI-668 (Presidio)
Elbasvir (Merck)
ACH-3102 (Achillion)
NS5B nucleoside/nucleotide inhibitors:
Mericitabine (Roche)
ACH-3422 (Achillion)
NS5B non-nucleoside inhibitors:
GS-9669 (Gilead)
ABT-072 (AbbVie)
Setrobuvir (Roche)

*Sofosbuvir/velpatasvir will be effective for all genotypes and may replace sofosbuvir/ledipasvir (Harvoni) in 2016 as the most commonly used medication for hepatitis C.

pegylated interferon and ribavirin. A fourth protease inhibitor, parita previr/r, is approved only as part of the interferon-free regimen (Viekira Pak).

Simeprevir, a second-generation protease inhibitor, has several advantages over telaprevir and boceprevir. Simeprevir is given once daily, can be taken with or without food, has a better side effect profile, has fewer drug-drug interactions, and is associated with higher cure rates. However, it is more expensive than telaprevir and boceprevir ($66,000 for three months). In addition, some people who have viral genotype 1a may have a preexisting viral mutation known as the Q80K mutation (which occurs in up to 30 percent of genotype 1a infections), and this mutation may decrease the cure rates.

Because of their lower cure rates, safety issues, side effect profiles, and serious drug interactions, it is unlikely that telaprevir and boceprevir will continue to be used in the United States. Table 15.4 shows dose, duration, and cure rates for the protease inhibitors.

Boceprevir has a complicated treatment protocol, requiring a lead-in phase of 4 weeks during which people are treated with only pegylated interferon and ribavirin. After 4 weeks, boceprevir is added to the regimen, and the duration of treatment with three drugs is determined by the presence of cirrhosis or previous nonresponse to a pegylated interferon and ribavirin combination. The treatment regimen for telaprevir and simeprevir includes three drugs for the first 12 weeks followed by a variable duration with pegylated interferon and ribavirin.

People undergoing treatment with protease inhibitors should adhere to the following guidelines:

- Do not use protease inhibitors alone; always in combination with interferon or other direct-acting antiviral drugs. If protease inhibitors are used alone, drug resistance will develop rapidly because they have a low barrier to resistance.
- Do not modify the dose or any of the drugs.
- Inform the physician of all medications used, including vitamins and herbal supplements (for example, St. John's wort can influence blood levels of protease inhibitors). These substances can interact

with other drugs and may increase or decrease the blood levels of protease inhibitors or other medications.

- Do not use protease inhibitors, especially in combination with ribavirin, if pregnant or planning pregnancy or for six months after childbirth, because of the risk of serious birth defects.

Table 15.4. Treatment with Protease Inhibitors, Interferon, and Ribavirin

Drug	*Dose and Duration*	*Cure Rates*
Telaprevir (Incivek)	750 mg three times daily with 25 grams of fat-containing meal Three drugs for 3 months, then interferon and ribavirin only *Duration:* 6 to 12 months (response-guided therapy)	Treatment-naive: 79% Treatment-naive with cirrhosis: 62% African American: 62%
Boceprevir (Victrelis)	800 mg three times daily with food (no need for fatty meal) 0 to 4 weeks: interferon and ribavirin only (lead-in phase) At week 4: add boceprevir. Continue for weeks 5 to 28 or weeks 5 to 36 (28 weeks if HCV RNA is negative at weeks 8 and 24, 36 weeks if HCV RNA is positive at week 4 and negative at week 24) *Duration:* 7 to 12 months (response-guided therapy) based on response *Modified regimen:* For nonresponders to interferon and ribavirin: three drugs from weeks 5 to 36, then interferon and ribavirin for weeks 37 to 48 For individuals who have cirrhosis: all three drugs for weeks 5 to 48	Treatment-naive: 66% Treatment-naive with cirrhosis: 52% African American: 53%
Simeprevir (Olysio)	150 mg daily with or without food Three drugs for 12 weeks and another 12 to 36 weeks of interferon and ribavirin *Duration:* 24 weeks for treatment-naive and relapsers, and 48 weeks for previous partial responders or nonresponders and people who have cirrhosis	Treatment-naive: 80% Treatment-naive with cirrhosis: 58% to 68%

Response Rates in People Who Have Cirrhosis

People who had cirrhosis showed a cure rate that increased by only 15 percent with the three-drug combination treatment when compared with pegylated interferon with ribavirin. Because most of the studies included only a small number of people who had cirrhosis, it is difficult to assess true response rates. Individuals who had cirrhosis had a lower response rate with protease inhibitors than treatment-naive people who had mild fibrosis. The reported cure rates are shown in table 15.5.

Side effects were more common in people who had cirrhosis in almost all studies with protease inhibitors, especially with boceprevir and telaprevir. Up to 50 percent of people who had cirrhosis and took either boceprevir or telaprevir had serious adverse events. Moreover, this drug combination was poorly tolerated by people who had cirrhosis and any previous complications, such as ascites, variceal bleeding, or encephalopathy.

The serious side effects were significantly lower with simeprevir-based treatment, but there is no experience of using this drug for people who have advanced cirrhosis (Child C score). Similarly, it is not indicated for use by people who have kidney failure (who undergo dialysis or have a glomerular filtration rate [GFR] of less than 30 ml/min/1.73 m^2).

Table 15.5. Use of Protease Inhibitors in Combination with Pegylated Interferon and Ribavirin for People with Hepatitis C Genotype 1 Virus Who Have Cirrhosis

Drug	*Cure Rates*
Telaprevir (Incivek)	Treatment-naive: 62% Relapsers: 84% Partial nonresponders: 34% Null responders: 14%
Boceprevir (Victrelis)	Treatment-naive: 42% to 52% Relapsers: 50% to 83% Partial nonresponders: 30% to 46%
Simeprevir (Olysio)	Treatment-naive: 58% to 65% Relapsers: 73% Partial nonresponders: 31% to 46%

Response Rates in People for Whom Pegylated Interferon and Ribavirin Treatment Failed

People who previously were nonresponders to pegylated interferon and ribavirin treatment, even individuals who had mild to moderate fibrosis, had lower cure rates when re-treated with a three-drug regimen containing protease inhibitors (table 15.6).

Duration of Treatment and Discontinuation Rules

The duration of treatment with telaprevir and boceprevir is based on a person's treatment response at weeks 4 to 12; this approach is known as response-guided therapy (table 15.7). For simeprevir, the duration of treatment is fixed at 24 weeks for individuals who are treatment-naive and for relapsers, and 48 weeks for nonresponders and people who have cirrhosis. People who have cirrhosis are not eligible for a shorter duration of therapy, based on early viral response, and are usually treated for 48 weeks.

Response-guided therapy is not applicable to all direct-acting antiviral drugs. Currently, telaprevir and boceprevir are the only two drugs approved for response-guided therapy. Clinical trials with telaprevir

Table 15.6. Use of Protease Inhibitors in Combination with Pegylated Interferon and Ribavirin for People with Hepatitis C Genotype 1 Virus Who Did Not Respond to Previous Treatment with Interferon and Ribavirin

Drug	*Cure Rates*
Telaprevir (Incivek)	Relapsers: 86% Partial nonresponders: 59% Null responders: 32%
Boceprevir (Victrelis)	Relapsers: 70% Partial nonresponders: 40% Null responders: 38%
Simeprevir (Olysio)	Relapsers: 77% Partial nonresponders: 65% Null responders: 53%

Table 15.7. Response-Guided Therapy

In response-guided therapy, the duration of treatment (6 or 12 months) and early discontinuation (futility of treatment) are based on viral count decrease during the early part of treatment (4 to 12 weeks). Response-guided therapy will reduce the risk of viral mutation (drug resistance), costs, and unnecessary side effects.

Table 15.8. Discontinuation Guidelines for Protease Inhibitors

Drug	*Indication for Discontinuation*
Telaprevir	1. HCV RNA levels of greater than or equal to 1,000 IU/ml at week 4 or 12; *or* 2. Detectable HCV RNA levels at week 24
Boceprevir	1. HCV RNA levels of greater than or equal to 1,000 IU/ml at week 12 (after 8 weeks with three drugs); *or* 2. HCV RNA levels of greater than or equal to 100 IU/ml at week 16 (after 12 weeks with three drugs); *or* 3. Detectable HCV RNA levels at week 28 (after 24 weeks with three drugs)
Simeprevir	1. HCV RNA levels of greater than or equal to 25 IU/ml at week 4 or 12 or at 24 weeks

showed that 58 percent of treatment-naive people who had undetectable virus in the blood at weeks 4 and 12 were eligible for shorter treatment duration (6 months), and the remaining people were treated for 48 weeks.

Because the risk of developing drug resistance is high when people who have an inadequate early response continue treatment with protease inhibitors, it is important to adhere to the guidelines shown in table 15.8 for all three protease inhibitors. When protease inhibitors are discontinued based on these rules, both interferon and ribavirin should also be discontinued.

Side Effects of Protease Inhibitors

Because protease inhibitors are currently used in combination with pegylated interferon and ribavirin, people experience the side effects of protease inhibitors as well as the side effects associated with pegylated interferon and ribavirin. Sometimes, distinguishing the side effects of these

drugs is difficult, but based on studies, the side effects associated with individual protease inhibitors have become better known.

Telaprevir and boceprevir are associated with significant and serious side effects, including rash, anemia, loss of taste, anorexia, and anorectal discomfort (table 15.9). Anemia is a serious side effect of these drugs (occurring in as many as 50 percent of individuals), and about 10 percent of individuals may require a blood transfusion. Up to 20 percent of people discontinue the medications because of the side effects. Steven-Johnson syndrome (a serious skin and systemic condition) is a rare (less than 1 in 200) and life-threatening condition that can occur with both boceprevir and telaprevir. Another condition that has been reported with telaprevir and, less frequently, with boceprevir is DRESS (drug rash, eosinophilia, systemic symptoms) syndrome (less than 1 in 200), and this also is a serious skin and systemic inflammatory condition. Early diagnosis and discontinuation of the protease inhibitor is essential to reduce fatality with both of these conditions.

Simeprevir is better tolerated, and less than 1 percent of people discontinued the medicine because of side effects. The common side effects with simeprevir are mild and may include fatigue, headache, rash (less common than with telaprevir), shortness of breath, and sensitivity to light (less than 4 percent). By applying sunscreen and reducing exposure to sun, this sensitivity can be managed effectively.

Drug-Drug Interactions

An enzyme system called CYP3A (cytochrome P450 3A) is involved in the elimination of many commonly used drugs. Protease inhibitors (to varying degrees, both telaprevir and boceprevir) are strong inhibitors of this enzyme system. This effect may increase blood levels of some commonly used medications that are normally eliminated by CYP3A.

Although simeprevir does not induce or inhibit CYP3A, it is metabolized by this enzyme system. Other drugs that stimulate or inhibit this enzyme system may either decrease or increase blood levels of the protease inhibitors, including simeprevir, or other medications. When other medications are used with protease inhibitors, it is important to confirm that there are no serious drug-drug interactions. Individuals should ob-

Table 15.9. Side Effects of Protease Inhibitors in Combination with Interferon and Ribavirin

Drug	*Major Side Effects*	*Rate of Discontinuation Because of Side Effects*
Telaprevir (Incivek)	Common: Drug rash (35%) Loss of appetite and taste Nausea Anorectal discomfort Anemia Rare (less than 1%): Steven-Johnson syndrome DRESS syndrome Other problems: serious drug-drug interactions	14%
Boceprevir (Victrelis)	Common: Anemia (up to 50%) Fatigue Loss of taste Less common: Rash Low white blood cells Hypersensitivity reaction Other problems: serious drug-drug interactions	13%
Simeprevir (Olysio)	Rare: Headache Fatigue Shortness of breath Itching Rash Photosensitivity Other problems: serious drug-drug interactions (less common and less serious than for telaprevir and boceprevir because it does not induce or inhibit CYP3A enzymes)	Less than 2%

tain a list of medications that have the potential for interactions from a physician, pharmacist, or the drug manufacturer's website.

> Drug-drug interactions: It is important to discuss with the physician the potential and serious drug-drug interactions when hepatitis C treatment is started with the newer, direct-acting antiviral drugs. Food supplements and herbal preparations may have an effect on the medications. Manufacturers' websites and a pharmacist can also provide this important information.

Despite the improved cure rates and less serious side effects for simeprevir compared with telaprevir and boceprevir, simeprevir is not likely to be used in combination with interferon and ribavirin in the future, given the availability of newer, safer drug combinations with higher cure rates and shorter treatment duration (see chapter 16).

Interferon and Ribavirin Combined with Sofosbuvir (NS5B Nucleotide Inhibitor) for Genotypes 1 and 4

Sofosbuvir, an NS5B nucleotide inhibitor, has fewer side effects, a higher barrier to resistance, and a shorter duration of treatment, making this drug an attractive alternative for interferon-based treatment. Moreover, the treatment is not based on response-guided therapy because, in clinical studies, nearly all people (more than 99 percent) cleared the virus during treatment. Treatment failure was mostly because of relapses. In addition, the drug discontinuation rate was less than 1 percent. The main disadvantage with this treatment is the high cost ($84,000 for three months of treatment, or $1,000 per pill).

Current treatment regimens containing sofosbuvir that have been approved by the FDA according to genotype are listed in table 15.10. Doses, treatment duration, and cure rates are summarized in table 15.11.

Currently, there are no data to support sofosbuvir with interferon and ribavirin for genotypes 5 and 6, but it may be effective. Just as with protease inhibitors, sofosbuvir should not be used alone.

Table 15.10. Treatment Guidelines for Sofosbuvir

Treatment Group	*Treatment Regimen*	*Notes*
People with genotype 1 and 4 infections	Sofosbuvir in combination with interferon and ribavirin	—
People with hepatitis C and HIV co-infection	Sofosbuvir in combination with interferon and ribavirin	This treatment regimen has not been tested for this group, but it has been approved based on the drug's safety profile.
People with genotype 2 and 3 infections	Sofosbuvir in combination only with ribavirin	A small study of 39 people showed that 12 weeks of treatment with both interferon and ribavirin could cure up to 97% of those who had genotype 3, but this treatment has not been approved.
People who have not responded to previous treatment with pegylated interferon and ribavirin	Sofosbuvir in combination with interferon and ribavirin	Although this treatment regimen has not been studied for this group, the FDA has predicted that 70% of nonresponders may be cured by this treatment.

> Sofosbuvir is not approved for use by people who have advanced liver failure or end-stage renal failure (GFR less than 30 ml/min/1.73 m^2) or those who have received an organ transplant.

The clinical trials showed that almost all people (nearly 100 percent) cleared the virus during treatment; failures were caused by relapses when treatment was discontinued. A few people who had cirrhosis were included in the study and had 80 percent cure rates. The study results are summarized in table 15.12.

Table 15.11. Dose and Duration of Treatment with Sofosbuvir with Interferon and Ribavirin

Dose and Duration	*Cure Rates*
12 weeks:	Treatment-naive:
Sofosbuvir 400 mg daily	Genotype 1: 89%
Pegylated interferon	Genotype 1a: 92%
Weight-based ribavirin:	Genotype 1b: 82%
Less than 75 kg, 1,000 mg daily	Genotype 4: 96%
More than 75 kg, 1,200 mg daily for 12 weeks	

Table 15.12. Results of Clinical Trials of Sofosbuvir in Combination with Pegylated Interferon and Ribavirin

Approximately 92% of people with genotype 1 infection who did not have cirrhosis were cured.
Approximately 87% of African Americans were cured.
Approximately 80% of treatment-naive people who had cirrhosis were cured (number of people treated was small).
IL28B genetic mutation or race did not significantly influence treatment response.
Almost all people cleared the virus during treatment, and failures to clear were caused by relapses.
Minimal side effects included headache, fatigue, and insomnia from sofosbuvir, and less than 1% discontinued treatment. Sofosbuvir does not cause anemia more than is expected from interferon and ribavirin.
To date, there are no reports of clinically significant drug resistance with sofosbuvir.

Drug-Drug Interactions

Sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007, which accounts for more than 90 percent of drug-related systemic exposure. The medications and supplement listed in table 15.13 should not be used during treatment with sofosbuvir because they cause a decreased concentration of sofosbuvir and GS-331007, leading to a reduced therapeutic effect of the drug.

Table 15.13. Medications to Avoid during Treatment with Sofosbuvir

Anticonvulsants (medications to control seizures):
Carbamazepine
Phenytoin
Phenobarbital
Oxcarbazepine
Anti-mycobacterials (medications for treating tuberculosis)
Rifabutin
Rifampin
Rifapentine
Herbal supplement:
St. John's wort (*Hypericum perforatum*)
HIV protease inhibitor:
Tipranavir with ritonavir

> Co-administration of any of the drugs shown in table 15.13 with sofosbuvir is not recommended, as it will decrease blood levels of sofosbuvir and its active metabolites.

Drugs that are potent P-gp (P-glycoprotein) inducers in the intestine (for example, rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir, so they should not be used with sofosbuvir.

> No dose adjustment is necessary for the HIV drugs darunavir + ritonavir, efavirenz, emtricitabine, raltegravir, rilpivirine, and tenofovir; for methadone; or for the anti-rejection drugs cyclosporine and tacrolimus.

Precautions

Although sofosbuvir is listed as safe for use during pregnancy (classified as a pregnancy class B drug), it should *not* be used during pregnancy because it is used with ribavirin. Similarly, it is not recommended for nursing mothers (table 15.14).

Table 15.14. Conditions in Which Sofosbuvir Should Not Be Used

Pregnancy
Nursing
Severe liver disease (Child B or C)
End-stage kidney disease (glomerular filtration rate less than 30 ml/min/1.73 m^2) or hemodialysis

Interferon and Ribavirin Combined with Daclatasvir (NS5A Nucleotide Inhibitor) for Genotype 1

The use of daclatasvir, an NS5A nucleotide inhibitor, in combination with ribavirin has not yet been approved by the FDA, but based on the cure rates reported in clinical trials (approximately 60 percent for genotype 1 infection with 24 weeks of treatment), it is unlikely to be used even if the FDA approves this combination.

- Before interferon-free regimens were approved in late 2014, the standard of care for people with hepatitis C genotypes 1 and 4 was sofosbuvir in combination with pegylated interferon and weight-based ribavirin for 12 weeks. This combination can be safely used for people co-infected with HIV.
- Sofosbuvir-based treatment has an excellent cure rate and safety profile.
- Sofosbuvir is very expensive and may not be affordable for the majority of people who have hepatitis C worldwide.
- If a protease inhibitor is used in combination with interferon and ribavirin, simeprevir is the drug of choice.
- In the United States, interferon-based treatment was replaced by interferon-free treatment by the end of 2014; this treatment regimen is discussed in chapter 16.

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Interferon-Free Treatment of Hepatitis C

During the past five years, the treatment of hepatitis C has advanced rapidly. The introduction of direct-acting antiviral drugs in 2011 improved cure rates. However, several of these direct-acting antiviral drugs, especially in combination with interferon and ribavirin, continue to be plagued by low rates of adherence to treatment and serious side effects, combined with the side effects and risks of anemia posed by interferon and ribavirin. In addition, interferon-based treatment is poorly tolerated by people who have depression, cirrhosis, renal failure, or anemia, and by individuals who have autoimmune disorders, and it cannot be used for people who have advanced liver disease. Because more than 70 percent of people who have hepatitis C in the United States have viral genotype 1, effective interferon-free treatment regimens for individuals with this viral genotype are essential.

The ideal interferon-free, direct-acting antiviral drug regimen should have the following properties:

- High potency
- High genetic barrier to resistance
- Effectiveness for all genotypes
- Once-daily or twice-daily oral dosing
- Minimal side effects
- Short treatment duration (4 to 12 weeks)
- Few drug-drug interactions
- Low cost

The currently available classes of direct-acting antiviral drugs, along with their properties, include

- *Protease inhibitors:* High potency; genotype-specific; low genetic barrier to resistance. Future generations of protease inhibitors may be effective against all genotypes.
- *NS5A inhibitors:* High potency; some are genotype-specific or variable, and some are effective against all genotypes; intermediate genetic barrier to resistance.
- *NS5B nucleotide or nucleoside polymerase inhibitors:* Intermediate potency; effective against all genotypes; high genetic barrier to resistance.
- *NS5B non-nucleoside inhibitors:* Intermediate potency; genotype-specific; low genetic barrier to resistance.

Interferon-free regimens for genotype 1, 2, and 3 infections were recently approved by the Food and Drug Administration, and there are many more in phase 2 and 3 trials. Most of these combinations have shown a cure rate of more than 90 percent for individuals who have viral genotypes 1a or 1b, with a treatment duration ranging from 8 to 24 weeks. These drug combinations use varying combinations of two or three classes of drugs: second-generation NS3 protease inhibitors, NS5A inhibitors, and nucleotide/nucleoside or non-nucleoside NS5B polymerase inhibitors. Some drug combinations include ribavirin and others do not.

This chapter describes the direct-acting antiviral drug combinations that are already approved or are likely to be approved in 2014–15. A detailed review of all reported studies of direct-acting antiviral drug combinations is beyond the scope of this book.

NS5B Nucleotide Inhibitor Sofosbuvir and Ribavirin

Sofosbuvir (Sovaldi) is an NS5B nucleotide inhibitor with activity against all viral genotypes; it has minimal side effects, has very few drug-drug interactions, and is given once daily with or without food. It has a high barrier to drug resistance, which makes it an excellent treatment for hep-

Table 16.1. Sofosbuvir and Ribavirin in the Treatment of Hepatitis C

Approved for genotype 2 infection (for 12 weeks) and for genotype 3 (for 24 weeks).
Approved for people who have hepatitis C genotype 1 and are interferon-ineligible, for 24 weeks.
Approved for people who have hepatitis C genotype 1, are interferon-ineligible, have liver cancer, and are awaiting liver transplantation, for up to 48 weeks or until transplantation, to reduce the risk of reinfection.

atitis C. The FDA approved sofosbuvir in December 2013 to be used with ribavirin (no interferon) for hepatitis C genotypes 2 and 3 (table 16.1). The treatment duration is 12 weeks for genotype 2 and 24 weeks for genotype 3. In December 2013, sofosbuvir was also approved in combination with both interferon and ribavirin for 12 weeks for genotypes 1 and 4. For individuals with genotype 1 who are ineligible for interferon treatment, the FDA approved sofosbuvir in combination with ribavirin for 24 weeks.

In October 2014, the FDA approved sofosbuvir in combination with the NS5A inhibitor ledipasvir (a single pill containing both drugs, marketed as Harvoni) for genotype 1 infection, and in November 2014, it approved sofosbuvir (Sovaldi) in combination with simeprevir (Olysio) for genotype 1. In December 2014, a three-drug regimen containing paritaprevir/r (protease inhibitor with ritonavir), ombitasvir (NS5A inhibitor), and dasabuvir (NS5B non-nucleoside inhibitor)—a combination marketed as Viekira Pak—with or without ribavirin was approved for individuals with genotype 1 infection, including those with compensated cirrhosis, HIV, or a liver transplant. No dosage adjustment is necessary with this combination for people with mild, moderate, or severe kidney failure, and possibly in patients undergoing dialysis, based on preliminary studies.

Although the combination of sofosbuvir and ribavirin is excellent for individuals who have genotype 2 infection, cure rates were found to be lower (77 percent) for individuals with genotype 3 for whom previous treatment had failed; cure rates were also lower (60 percent) for those with genotype 3 infection and cirrhosis. Cure rates were predicted to be lower for individuals who have genotype 1 and are awaiting liver trans-

Table 16.2. Hepatitis C Cure Rates with Sofosbuvir and Ribavirin

Virus Genotype	*Duration of Treatment*	*Cure Rates*
Genotype 1	24 weeks	Treatment-naive, HIV and hepatitis C co-infection, and no cirrhosis: 76%
Genotype 2	12 weeks	No cirrhosis: 90% Cirrhosis: ~80% Treatment-experienced: 88%
Genotype 3	24 weeks	Treatment-naive without cirrhosis: 93% Treatment-experienced: 77% Treatment-experienced with cirrhosis: 60%
Genotype 4 (small phase 2 study)	12 weeks	Treatment-naive: 79% Treatment-experienced: 59%
	24 weeks	Treatment-naive: 100% Treatment-experienced: 87%

plantation and for those who cannot tolerate treatment with interferon (approximately 70 percent, based on experience with HIV and hepatitis C treatment).

Only a small number of people who have viral genotypes 2 and 3 and have cirrhosis, especially those who have had previous treatment, were studied in clinical trials with sofosbuvir and ribavirin, thus it is difficult to predict the treatment response. For individuals who have genotype 1 infection and compensated cirrhosis, there is not enough evidence to support treatment with sofosbuvir and ribavirin. Similarly, more data are required for individuals who have genotype 4 infection. The results for treatment outcomes for all hepatitis C genotypes are summarized in table 16.2.

Protease Inhibitor Simeprevir and NS5B Nucleotide Inhibitor Sofosbuvir

Many physicians have started treating people who have more advanced liver disease with simeprevir and sofosbuvir (without interferon and ribavirin) and have observed cure rates of more than 90 percent with

12 weeks of treatment. This treatment regimen was approved by the FDA in November 2014 for individuals who have the genotype 1 infection.

In a small clinical trial (less than 200 individuals) of people who had genotype 1 infection, the participants were treated with simeprevir and sofosbuvir for either 12 or 24 weeks; in addition, some were also given ribavirin. The study results (table 16.3) showed the following:

- Individuals had high cure rates irrespective of addition of ribavirin or treatment duration. All study participants who had genotype 1b infection were cured; nonresponse was observed only in individuals who had genotype 1a (especially with the Q80K mutation).
- Participants experienced mild side effects, including fatigue, headache, nausea, insomnia, rash, and, rarely, photosensitivity.
- The drug discontinuation rate was low (less than 2 percent, primarily in the 24-week treatment group).

Simeprevir and sofosbuvir are costly; the combined cost of the drugs is $150,000 for 12 weeks of treatment. Moreover, this treatment regimen has not been tested in people who have liver and kidney failure. In addition, more recent studies report lower cure rates for people who have advanced cirrhosis (90 percent for Child A and 75 percent for Child B).

Table 16.3. Hepatitis C Cure Rates with Simeprevir and Sofosbuvir, with or without Ribavirin

	Cure Rate (weeks of treatment)	
Treatment Group	*Simeprevir and Sofosbuvir*	*Simeprevir and Sofosbuvir with Ribavirin*
People with genotype 1 infection and mild fibrosis (previous null response to interferon and ribavirin)	93% (12 weeks) 93% (24 weeks)	96% (12 weeks) 79% (24 weeks)
People with genotype 1 infection and advanced fibrosis (both treatment-naive and previous null response to interferon and ribavirin)	93% (12 weeks) 100% (24 weeks)	93% (12 weeks) 93% (24 weeks)

This combination is unsafe for people who have Child C cirrhosis or those with jaundice. Physicians are unlikely to continue to use this treatment regimen since more efficacious and less costly options have become available.

NS5B Nucleotide Inhibitor Sofosbuvir and NS5A Inhibitor Ledipasvir (Harvoni)

A combined pill containing two drugs—sofosbuvir (400 mg) and ledipasvir (90 mg), the latter an NS5A inhibitor with activity against genotype 1 (variable for other genotypes)—developed by Gilead Sciences can be taken once daily with or without food for 8 or 24 weeks. This combination pill was approved by the FDA in October 2014. Clinical studies of the Gilead regimen show high cure rates, minimal side effects, and low drug discontinuation rates in several different groups of individuals with genotype 1 virus (table 16.4). Treatment response was similar among individuals who had viral genotypes 1a and 1b, and side effects were minimal.

For people who had cirrhosis and for whom a previous interferon-based regimen in combination with a protease inhibitor had failed, the cure rate was 90 percent when treated with Harvoni for 12 weeks, but

Table 16.4. Sofosbuvir and Ledipasvir Treatment for Hepatitis C Genotype 1

Treatment Group (all with genotype 1 virus)	*Cure Rate*
Treatment-naive people, with or without cirrhosis, 12 or 24 weeks' duration, with or without ribavirin	97% to 99%
Treatment-naive people, without cirrhosis, 8 weeks' duration	93%
Nonresponders to previous treatment, without cirrhosis, 12 weeks' duration; nonresponders included previous treatment failure with:	94% to 96%
Pegylated interferon and ribavirin	
Pegylated interferon, ribavirin, and telaprevir or boceprevir	
Nonresponders to previous treatment with pegylated interferon and ribavirin, with cirrhosis:	
12 weeks' duration	82% to 86%
24 weeks' duration	Nearly 99%

when treated with Harvoni and ribavirin, the cure rate increased to 96 percent, suggesting that addition of ribavirin may be useful in such cases.

In a small study (108 participants), when people with decompensated cirrhosis (Child B and Child C cirrhosis) were treated with Harvoni and ribavirin for 12 weeks, 86 percent were cured. Cure was associated with an improvement in liver disease in many participants. Despite this encouraging report, this combination needs to be used with caution for people with advanced cirrhosis and should be used only under the careful guidance of a liver specialist.

Harvoni with ribavirin was tested in 223 liver transplant recipients with hepatitis C. In the absence of advanced cirrhosis, 12 weeks of treatment cured 96 percent of these individuals, but with Child B cirrhosis the cure rate was 85 percent, and with Child C it was 60 percent.

In a study of 51 people who had previously received sofosbuvir-based treatment (25 with interferon, ribavirin, and sofosbuvir; 21 with sofosbuvir and ribavirin; and 5 with sofosbuvir alone), 50 were cured when treated with Harvoni in combination with ribavirin for 12 weeks.

The results from a small study (50 participants) of people who had HIV and hepatitis C co-infection showed that treatment with Harvoni is equally effective (cure rate 98 percent) for people who have HIV.

Another small study of individuals who had genotype 3 infection showed that the treatment could be very effective if used in combination with ribavirin for 12 weeks. For people whose previous treatment had failed, Harvoni in combination with ribavirin cured 89 percent (25 of 28) of those without cirrhosis and 73 percent (16 of 22) of those with cirrhosis. The cure rates with Harvoni treatment for 12 weeks for those with genotype 4 infection (19 of 20, or 95 percent) and genotype 6 infection (24 of 25, or 96 percent) were also excellent, indicating that this combination could be used for non–genotype 1 infections—although, currently, it is approved only for genotype 1 infection. It has not been approved for people who have co-infection with hepatitis C and HIV or for liver transplant recipients.

The regimen that was approved in October 2014 for treatment of hepatitis C genotype 1 is shown in table 16.5. The cost of this treatment

Table 16.5. Sofosbuvir and Ledipasvir Regimen for Treatment of Hepatitis C Genotype 1

Treatment Group	*Duration*
Genotype 1: no cirrhosis and viral count less than 6 million IU/ml	8 to 12 weeks
Genotype 1: with or without cirrhosis and viral count more than 6 million IU/ml	12 weeks
Genotype 1: treatment-experienced with cirrhosis and failed interferon-based treatment with or without protease inhibitors	24 weeks

regimen for 12 weeks is $94,000. The dosing is one pill daily with or without food. Drug-drug interactions with Harvoni are few (table 16.6), but St. John's wort should not be taken with this medicine.

Summary of Treatment with Ledipasvir and Sofosbuvir

- The combination of ledipasvir and sofosbuvir (Harvoni) can cure more than 95 percent of people with genotype 1 infection.
- Duration of treatment can be 8 to 12 weeks for treatment-naive people.
- Treatment-experienced people without cirrhosis can expect 95 percent cure rates with 12 weeks of treatment.
- Treatment-experienced people with cirrhosis may need to be treated for 24 weeks to get higher than 95 percent cure rates.
- Treatment can be equally effective for people for whom a three-drug regimen containing interferon, ribavirin, and a protease inhibitor has failed.
- Although not approved by the FDA, this treatment could be used for liver transplant recipients, people co-infected with HIV, and those with other viral genotypes, including genotypes 3, 4, and 6.
- Side effects are minimal (serious drug-related adverse events occur in less than 1 percent), and the drug discontinuation rate is less than 1 percent.
- It is unsafe to use this combination treatment for people who have renal failure or who take amiodarone.

Table 16.6. Safety of Other Medications with Harvoni

Medications that should not be used with Harvoni

The following drugs may reduce or increase the blood levels of medications and decrease the effectiveness of Harvoni or cause toxicity:

- Antiarrhythmics: amiodarone
- Anticonvulsants (seizure medication): carbamazepine, phenytoin, phenobarbital, oxcarbazepine
- Anti-mycobacterials (treatment for tuberculosis): rifabutin, rifampin, rifapentine
- Hepatitis C treatments (other treatment): simeprevir (Olysio)
- Herbal supplements: St. John's wort
- HIV antiretrovirals: Stribild (combination of elvitegravir, cobicistat, emtricitabine, and tenofovir DF), tipranavir-ritonavir combination
- Statins (cholesterol medication): rosuvastatin

Medications that can be used with caution

Acid-reducing agents: An increase in gastric pH will decrease the concentration of ledipasvir. Therefore, the following medications need to be used with caution and the dosage adjusted:

- Antacids (e.g., aluminum and magnesium hydroxide) should not be used for 4 hours before or after taking Harvoni.
- H_2 receptor antagonists (e.g., famotidine, ranitidine, cimetidine) should be used at lower doses.
- Proton-pump inhibitors (e.g., omeprazole, esomeprazole) should be used at lower doses.

Digoxin:

- Check digoxin levels, because Harvoni may increase digoxin levels in the blood.

HIV medications:

- Tenofovir-containing regimens should be used with caution (combinations of tipranavir and ritonavir with tenofovir, such as efavirenz-emtricitabine-tenofovir DF [Atripla], should be avoided).
- Regimens containing tenofovir DF (VIREAD) and an HIV protease inhibitor–ritonavir combination—including atazanavir-ritonavir + emtricitabine-tenofovir DF (Truvada); darunavir-ritonavir + emtricitabine-tenofovir DF; lopinavir-ritonavir (Kaletra) + emtricitabine-tenofovir DF—should be used with caution.

Medications that can be used safely

Calcium channel blockers (blood pressure medication): verapamil

HIV medications:

- Abacavir
- Atazanavir-ritonavir (when not used with tenofovir)
- Darunavir-ritonavir (when not used with tenofovir)
- Efavirenz

(continued)

Table 16.6. Safety of Other Medications with Harvoni, *continued*

Emtricitabine
Lamivudine
Raltegravir
Rilpivirine
Tenofovir (when not used with other HIV medications)
Immunosuppressants (medications used by transplant recipients): cyclosporine, tacrolimus
Opioids: methadone
Oral contraceptives
Statins (cholesterol medication): pravastatin

Interferon-Free Regimen with Three Direct-Acting Antiviral Drugs

An interferon-free drug regimen developed by AbbVie Pharmaceuticals (marketed as Viekira Pak) comprises three direct-acting antiviral drugs:

- Two pills, taken *once daily with food (without regard to fat or calories)*, each pill containing:
  - Protease inhibitor paritaprevir 75 mg combined with the HIV antiviral drug ritonavir 50 mg (a combination called paritaprevir/r; ritonavir is added to boost blood levels of paritaprevir)
  - NS5A inhibitor ombitasvir 12.5 mg
- One pill, taken *twice daily*, containing NS5B non-nucleoside inhibitor dasabuvir 250 mg.
- With or without ribavirin, depending on viral genotype subtype, *twice daily*, dose based on body weight.

Clinical trials of this AbbVie treatment regimen (Viekira Pak) for 12 to 24 weeks in treatment-naive people without cirrhosis showed

- High cure rates (table 16.7)
- Low treatment failure rate (0.2 percent) and relapse rate (1.5 percent)

Table 16.7. Cure Rates with the AbbVie Regimen Used for 12 weeks for Treatment-Naive Individuals with Hepatitis C Genotype 1 and without Cirrhosis

Cure rates for genotype 1b infection with or without ribavirin were 99.5% and 99%, respectively.
Cure rates for genotype 1a infection were higher with ribavirin (97%) than without ribavirin (90%); for genotype 1a, viral relapse was 7.8% without ribavirin and 2.0% with ribavirin.

- Low discontinuation rate caused by adverse events (0.6 percent)
- Mild side effects, including nausea, itching, insomnia, diarrhea, and weakness and fatigue

A moderate reduction (2.4 g/dl reduction) in hemoglobin occurred in 5.8 percent of study participants, and this decrease was attributed to ribavirin. Hemoglobin reduction in those who did not take ribavirin was less than 0.5 g/dl. Side effects were more commonly reported by people who took ribavirin with other medications. The common side effects were itching, fatigue, nausea, and insomnia, and these side effects were less common in those who did not take ribavirin.

Cure rates were excellent for treatment-naive people with genotype 1 infection and without cirrhosis. The FDA approved the AbbVie regimen (Viekira Pak) with ribavirin for people who have genotype 1a infection; the duration of treatment is 12 weeks for those without cirrhosis and 24 weeks for those with cirrhosis. For genotype 1b, the recommendation is treatment without ribavirin for 12 weeks for those without cirrhosis and treatment with ribavirin for 12 weeks for those with cirrhosis.

The AbbVie treatment regimen was also tested in several other groups of individuals, with favorable results. A summary of the clinical trial results is given in table 16.8. The major aspects of the AbbVie treatment are summarized in table 16.9.

Table 16.8. Results of AbbVie Regimen (Viekira Pak), with or without Ribavirin, for Hepatitis C Virus Genotypes 1a and 1b

Treatment Group	*Cure Rate (treatment duration)*
Treatment-experienced with genotype 1a and 1 b infection with cirrhosis	
Treatment-naive and treatment-experienced people with genotype 1a	89% (12 weeks) 94% (24 weeks)
Treatment-naive and treatment-experienced people with genotype 1b	99% (12 weeks)
Null responders to previous interferon and ribavirin treatment (12 weeks)	86.7%
Null responders to previous interferon and ribavirin treatment (24 weeks)	95.2%
Null responders with genotype 1a (12 weeks)	80%
Null responders with genotype 1a (24 weeks)	92.9%
Null responders with genotype 1b (12 or 24 weeks)	100%
Treatment-experienced with genotype 1a and 1b infection without cirrhosis	
Relapsers	95.3%
Partial responders	100%
Null responders	95.2%

Table 16.9. AbbVie Regimen (Viekira Pak), with or without Ribavirin, for People Infected with Hepatitis C Virus Genotype 1

Genotype 1a:

No cirrhosis: AbbVie regimen with ribavirin for 12 weeks
With cirrhosis: AbbVie regimen with ribavirin for 24 weeks

Genotype 1b:

No cirrhosis: AbbVie regimen without ribavirin for 12 weeks (even for individuals with previous treatment failure)
With cirrhosis: AbbVie regimen with ribavirin for 12 weeks

Note: Treatment for people who have HIV should be similar to that for people without HIV. Liver transplant recipients should be treated for 24 weeks with ribavirin, and immunosuppression should be adjusted and ribavirin dose reduced. People who have renal failure could be treated with this regimen, but the ribavirin dose needs to be reduced. It is not indicated for people with advanced liver failure (Child B and C cirrhosis).

Comparison between Gilead and AbbVie Regimens for Genotype 1 Infection

The clinical trials showed that the AbbVie regimen is comparable to the Gilead regimen of ledipasvir and sofosbuvir in terms of cure rates for both genotype 1a and 1b infections, but there are some differences, mostly in terms of drug-drug interactions and the need for ribavirin for genotype 1a infection and for people who have cirrhosis (both 1a and 1b). Drug-drug interactions with the AbbVie regimen are common (table 16.10), because of the protease inhibitor (paritaprevir) and the ritonavir (added to increase the blood levels and half-life of paritaprevir, enabling once-daily dosing). As with telaprevir and boceprevir, this combination inhibits CYP3A enzymes, which will affect other drugs taken with the AbbVie regimen. Adding ribavirin may also lead to anemia, especially in people who have cirrhosis. In addition, contraceptive pills containing ethinyl estradiol should be discontinued by women who are taking Viekira Pak, and alternative contraceptives should be used. Nevertheless, the AbbVie treatment combination is safe and effective. A comparative analysis of the Gilead (Harvoni) and AbbVie (Viekira Pak, with or without ribavirin) regimens is shown in table 16.11.

Table 16.10. Safety of Other Medications with Viekira Pak

Medications that should not be used with Viekira Pak
The following drugs may reduce or increase the blood levels of medications and decrease the effectiveness of Viekira Pak or cause toxicity:
Anticonvulsants (seizure medication): carbamazepine, phenytoin, phenobarbital
Anti-mycobacterials (treatment for tuberculosis): rifampin
Antihypertensives (blood pressure control): alfuzosin HCl
Antipsychotic medications: pimozide
Contraceptives: ethinyl estradiol–containing contraceptives
Herbal supplements: St. John's wort
HIV antiretrovirals: efavirenz
Migraine medications: ergotamine, dihydroergotamine, ergonovine, methylergonovine

(continued)

Table 16.10. Safety of Other Medications with Viekira Pak, *continued*

Sedatives: triazolam, oral midazolam

Statins (cholesterol medication): lovastatin, simvastatin

Other medications for cholesterol and triglycerides: gemfibrozil

Other medications: phosphodiesterase-5 (PDE5) inhibitor sildenafil (ingredient of Viagra) when used in higher doses to treat pulmonary hypertension

Medications that can be used with caution

Acid-reducing agents:

Proton-pump inhibitor: omeprazole dose should be increased

Anti-arrhythmics (heart rate control): amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine

Antifungals: ketoconazole, voriconazole

Antihypertensives (blood pressure control): amlodipine dose should be reduced

Asthma medications: salmeterol should be avoided

Diuretics: furosemide dose should be adjusted

HIV medications:

Atazanavir-ritonavir, darunavir-ritonavir, lopinavir-ritonavir (these combinations are not recommended)

Rilpivirine is not recommended

Immunosuppressants: cyclosporine (one-fifth of regular dose); tacrolimus (0.5 mg every 5 to 7 days) dose should be drastically reduced

Narcotics: buprenorphine-naloxone can be used but needs to be closely monitored for sedative and cognitive side effects

Sedatives: alpazolam dose should be reduced

Steroid nasal sprays: fluticasone nasal spray should be used with caution or avoided

Statins: rosuvastatin (maximum dose 10 mg daily), pravastatin (maximum dose 40 mg daily)

Medications that can be used safely

Antidepressants: duloxetine, escitalopram

Blood thinners: warfarin

Heart medications: digoxin

HIV medications:

Emtricitabine-tenofovir fumarate (Truvada)

Raltegravir

Opioids: methadone

Progestin-only oral contraceptives

Sleep medications: zolpidem

Table 16.11. Comparison of Gilead and AbbVie Regimens for Hepatitis C Genotype 1

Characteristic	*Ledipasvir-Sofosbuvir (Gilead regimen)*	*Paritaprevir-Ritonavir-Ombitasvir + Dasabuvir ± Ribavirin (AbbVie regimen)*
Cost	$94,000 for 12 weeks	$83,319 for 12 weeks
Pill burden	One pill	Several pills
Efficacy	More than 95%	More than 95%
Duration	8 to 12 weeks; could be shortened to 8 weeks for people who do not have cirrhosis	12 to 24 weeks; may need 24 weeks for people who have genotype 1a and have cirrhosis
Side effects	Low	Low, except when ribavirin is used
Anemia	None	None without ribavirin, mild to moderate with ribavirin
Drug-drug interaction	Low	Moderate
Genotype	Only genotype 1	Only genotype 1

Unlike Harvoni, which cannot be used by people who have kidney failure, Viekira Pak can be used by people who have mild, moderate, or severe kidney failure without any dose adjustments. Use of this combination for people who undergo dialysis has recently been studied. Since ribavirin is eliminated by the kidneys, ribavirin dose (200 mg/day or less) needs to be reduced for people with kidney dysfunction.

Other All-Oral Treatment Regimens

Other pharmaceutical companies are working to develop interferon-free regimens. Many of these combination treatments will be available in the next few years. Some promising combinations are discussed briefly here. In addition to the direct-acting antiviral drugs, host-targeted agents (agents targeted at a person's cellular proteins that are essential for viral replication, including cyclophilin inhibitors and antagonists of miRNA-122) are also in early clinical trials, and in the future, these

classes of drugs may be combined to shorten the treatment duration and achieve 100 percent cure rates.

Sofosbuvir and NS5A Inhibitor Daclatasvir

Bristol-Myers Squibb is working to develop a treatment regimen of sofosbuvir (Gilead Sciences) in combination with daclatasvir, an NS5A inhibitor that is effective against all hepatitis C virus genotypes. Theoretically, a combination of sofosbuvir and daclatasvir will be effective against all genotypes. Clinical trials have shown that this combination is effective and safe.

In a small study of people with genotype 1 infection for whom treatment with interferon, ribavirin, and telaprevir or boceprevir had failed, individuals were treated with sofosbuvir and daclatasvir with or without ribavirin for 24 weeks. All but one person (98 percent) were cured by this combination. However, 12 weeks of treatment with ledipasvir-sofosbuvir without ribavirin has been shown to cure 94 percent of people infected with genotype 1 for whom treatment with interferon, ribavirin, and telaprevir or boceprevir has failed. For this reason, sofosbuvir and daclatasvir combination treatment is unlikely to be developed further for genotype 1–infected people.

Sofosbuvir and daclatasvir for 12 to 24 weeks may be effective for genotypes 2, 3, and 4, but until more data are made available, no recommendations can be made regarding this treatment combination. A recent study examined the cure rates with this combination for 101 people who had received no previous treatment and 51 who had previous treatment experience. Both groups were treated for 12 weeks. The cure rates were 90 percent (91 of 101) for the treatment-naive group and 86 percent (44 of 51) for the treatment-experienced group. However, the cure rate was only 60 percent (16 of 27) for people with genotype 3 and cirrhosis. These findings suggest that this combination is not superior to other interferon-free regimens.

Asunaprevir, Daclatasvir, and Beclabuvir

Bristol-Myers Squibb has developed a three-drug treatment combination comprising

- NS3 protease inhibitor asunaprevir
- NS5A inhibitor daclatasvir
- NS5B non-nucleoside inhibitor Beclabuvir

The results of 12 weeks of this treatment regimen looked promising, but the regimen has several limitations. Cure rates (approximately 92 percent) were lower than for the Gilead and AbbVie regimens; individuals who had genotype 1b infection had higher cure rates with this regimen; and although side effects were minimal (less than 2 percent), the drug discontinuation rate was 4.8 percent in early trials. In addition, the medications have to be taken twice daily. The cost for this treatment has not been determined.

Asunaprevir and Daclatasvir in Treatment of Genotype 1b Infection

For individuals who have genotype 1b infection, the drug combination (developed by Bristol-Myers Squibb) consisting of NS3 protease inhibitor asunaprevir (100 mg twice daily) and NS5A inhibitor daclatasvir (60 mg once daily) for 24 weeks showed 90 percent cure rates for treatment-naive individuals and approximately 82 percent for null responders and partial responders to previous treatment and for individuals not able to tolerate interferon. The longer duration of treatment (24 weeks) and the availability of alternative treatment options with higher cure rates make this combination less attractive for treating individuals who have genotype 1b. Bristol-Myers Squibb is unlikely to develop this combination for the U.S. market.

Fixed Dose of Grazoprevir-Elbasvir (Single Tablet) without Ribavirin for 12 Weeks

This regimen, developed by Merck Pharmaceutical, is likely to be approved in 2016 and contains Grazoprevir (100 mg, NS3-4A protease inhibitor) and Elbasvir (50 mg, NS5A inhibitor). This once-daily, fixed dose regimen without ribavirin has shown excellent cure rates with minimal side effects in clinical trials in people with genotype 1, 4 and 6, with and without cirrhosis, in those who failed previous treatments, including boceprevir, telaprevir, and simeprevir, and in HIV/HCV infection. The reported cure rates range from 92 to 97 percent, with similar cure rates

in those with and without cirrhosis and in those with HIV. Preliminary data show that the treatment could be shortened to 8 weeks in people without cirrhosis and with genotype 1b infection. Most importantly, this regimen could be safely used in those with renal failure and on dialysis (in preliminary trials, 114 or 115 patients with genotype 1 were cured with 12 weeks of treatment). The side effects were minimal and included headache, fatigue, and nausea. In the clinical trials, drug discontinuation rate due to side effects was 1%. This combination, however, is not very effective for those with genotype 2, 3, or 5.

Treatment Options for Individuals Who Have Received Liver Transplants

People who receive organ transplants for hepatitis C–related liver disease or liver cancer can become reinfected with hepatitis C; the reinfection rate is 100 percent if individuals have hepatitis C RNA in their blood at the time of liver transplantation. Pegylated interferon and ribavirin are poorly tolerated by transplant recipients, and cure rates with this treatment are low (approximately 20 percent). A three-drug treatment regimen with pegylated interferon, ribavirin, and first-generation protease inhibitors, such as telaprevir or boceprevir, improved the cure rates but caused serious drug-drug interactions of telaprevir and boceprevir with immunosuppressive medications, including tacrolimus, cyclosporine, and rapamune.

Currently, the only approved medication to treat recurrent hepatitis C in people who have received a liver transplant is the AbbVie regimen. A small study conducted by AbbVie showed a 97 percent cure rate (33 of 34 people) with 24 weeks of treatment. If this regimen is used, the immunosuppressive medications need to be adjusted, and blood levels of immunosuppressive agents must be monitored closely. A fairly large clinical trial of sofosbuvir and ledipasvir (Harvoni) in combination with ribavirin for 12 weeks showed cure rates of 96 percent for people with mild fibrosis or Child A cirrhosis. Harvoni in combination with ribavirin is the preferred option for people who have a liver transplant. Treatment options, prevention of recurrence, and the natural progression of recurrent hepatitis C are further discussed in chapter 18.

Optimal Treatment Options in 2014–15

The rapid progress in hepatitis C therapy poses a challenge in accurately predicting the future of treatment. With the current developments, interferon-based treatment is unlikely to be used in the United States in the future, except for an occasional person for whom all other oral drug regimens fail. Table 16.12 suggests a treatment algorithm organized by viral genotype, based on the current evidence.

Table 16.12. Treatment Options for Hepatitis C, Based on Current Evidence

Treatment Group	*Treatment*
Genotype 1 Without cirrhosis Treatment-naive or treatment-experienced	*Preferred 1:* Ledipasvir-sofosbuvir (Harvoni) combination for 8 to 12 weeks Treatment-naive with high viral count (>6 million IU) or treatment- experienced: 12 weeks Treatment-naive and no cirrhosis with low viral count: 8 weeks *Preferred 2:* Paritaprevir-ritonavir-ombitasvir and dasabuvir with or without ribavirin (AbbVie regimen, Viekira Pak): With ribavirin for 12 weeks for genotype 1a Without ribavirin for 12 weeks for genotype 1b The cost and potential drug-drug interaction are factors that could be considered when choosing between the two options. *Alternative:* Sofosbuvir and simeprevir for 12 weeks (may be cost prohibitive)
Genotype 1 With cirrhosis Treatment-naive	*Preferred:* Ledipasvir-sofosbuvir (Harvoni) combination for 12 weeks *Alternative:* Paritaprevir-ritonavir-ombitasvir and dasabuvir (AbbVie regimen, Viekira Pak): With ribavirin for 24 weeks for genotype 1a. With ribavirin for 12 weeks for genotype 1b. For genotype 1a, ledipasvir-sofosbuvir (Harvoni) is preferred. For genotype 1b, the cost and potential drug-drug interaction are factors that could be considered when choosing between the two options. *Alternative:* Sofosbuvir and simeprevir for 12 weeks (may be cost prohibitive)

(continued)

Table 16.12. Treatment Options for Hepatitis C, Based on Current Evidence, *continued*

Treatment Group	*Treatment*
Genotype 1 With cirrhosis Treatment-experienced	*Genotype 1b:* *Preferred:* Paritaprevir-ritonavir-ombitasvir and dasabuvir (AbbVie regimen, Viekira Pak) with ribavirin for 12 weeks *Alternative:* Ledipasvir-sofosbuvir combination for 24 weeks or ledipasvir-sofosbuvir (Harvoni) with ribavirin for 12 weeks *Genotype 1a:* Ledipasvir-sofosbuvir for 24 weeks (or possibly for 12 weeks with ribavirin) Paritaprevir-ritonavir-ombitasvir and dasabuvir (AbbVie regimen, Viekira Pak) with ribavirin for 24 weeks Sofosbuvir-simeprevir for 12 weeks For genotype 1a, the cost, duration, and potential drug-drug interactions are factors that could be considered when choosing between the three options.
Genotype 2 With cirrhosis Treatment-naive or treatment-experienced	Sofosbuvir and ribavirin for 12 weeks
Genotype 3 With cirrhosis Treatment-naive or treatment-experienced	Sofosbuvir and ribavirin for 24 weeks More clinical trials and research are necessary for individuals with genotype 3 infection who have cirrhosis, and especially for previous nonresponders who have cirrhosis. *Alternative:* Interferon, ribavirin, and sofosbuvir for 12 weeks (not yet approved) could be an excellent alternative for people with well-compensated liver disease until further studies are available. Ledipasvir-sofosbuvir (Harvoni) with ribavirin for 12 weeks is another option. Sofosbuvir and daclatasvir with or without ribavirin for 12 weeks may become an option in the future if daclatasvir is approved by the FDA.
Genotype 4 Without cirrhosis Treatment-naive	*Preferred:* Sofosbuvir and ribavirin for 24 weeks (not yet approved and only limited data) *or* ledipasvir-sofosbuvir (Harvoni) for 12 weeks *Alternative:* Interferon, ribavirin, and sofosbuvir for 12 weeks (only FDA-approved option) could be an excellent alternative until further studies are available. Other less-studied options (not yet approved) are sofosbuvir-simeprevir or sofosbuvir-daclatasvir (both with or without ribavirin). More studies are needed for treatment-experienced individuals and those who have cirrhosis.

(continued)

Table 16.12. Treatment Options for Hepatitis C, Based on Current Evidence, *continued*

Treatment Group	*Treatment*
Genotype 5	No data on all-oral treatment; perhaps could be treated as for genotype 1.
Genotype 6	Ledipasvir-sofosbuvir for 12 weeks is a good option, based on limited data, *or* perhaps could be treated as for genotype 1.
Recurrent hepatitis C after liver transplantation	Only limited data are available and no treatments are approved. *Preferred:* Ledipasvir-sofosbuvir (Harvoni) with ribavirin for 12 weeks *Alternative:* Paritaprevir-ritonavir-ombitasvir and dasabuvir (AbbVie regimen) with ribavirin for 24 weeks *or* sofosbuvir and ribavirin for 24 weeks
Co-infection with HIV	Current data suggest that these individuals could receive the same treatment regimens as people who do not have HIV. Consider potential drug-drug interactions with HIV medications when choosing a treatment regimen.
Advanced liver failure (Child C cirrhosis)	No data to make recommendations.
Kidney failure	The AbbVie regimen is safe for people who have severe renal failure, but a lower dose of ribavirin should be used. There are limited data on people who undergo dialysis and are treated with the AbbVie regimen. Sofosbuvir is not recommended for individuals who are undergoing dialysis or have end-stage kidney disease. Grazoprevir/Elbasvir (Merck) without ribavirin will be the best option, after this combination is approved by the FDA.
Individuals who have multiple drug-resistant viral mutations	No data to make recommendations. More research is needed.

Challenges of Hepatitis C Treatment

The progress in treating hepatitis C is an important medical development. The cure rates improved from 6 percent with 6 months of standard interferon therapy in 1990 to more than 95 percent with 8 to 12 weeks of oral medications in 2014, with minimal side effects.

Several challenges, both for the healthcare community and for people who have hepatitis C, remain:

- Most people who have hepatitis C remain undiagnosed and will remain undiagnosed in most parts of the world that have limited healthcare systems.
- The current cost of treatment is high ($100,000 per treatment) and not affordable for most individuals.
- Improvements need to be made in treating individuals who have genotype 3 infection.
- Clinical trials should be conducted that include people who are on dialysis or have advanced liver failure (Child C). Trials also need to be done in children.
- Development of a vaccine to prevent new hepatitis C infections is needed.

Approval of additional treatment regimens is likely to reduce the costs of hepatitis C treatment and possibly help make these treatments available to low- and middle-income countries as well. Some pharmaceutical companies have already promised to make these drugs available in low- and middle-income countries at an affordable cost. Global eradication of hepatitis C may be theoretically possible with better prevention, widespread screening, and less expensive and safer drugs that have cure rates of nearly 100 percent and, perhaps, a short duration (4 weeks or less) of treatment.

17

Liver Transplantation

In 1963, Dr. Thomas Starzl performed the first liver transplantation. At first, liver transplantation was done only for people who had advanced liver cancer, and the results were poor. Since then, many improvements in organ preservation, surgical techniques, recipient selection, and immune system suppression have greatly increased the success of the procedure. In the past 20 years, liver transplantation has evolved into a viable option with excellent outcomes for many people who have end-stage cirrhosis, including cirrhosis caused by hepatitis C, and people who have liver cancer. Recent data from the United Network for Organ Sharing (UNOS) suggest that the one-year and five-year individual survival rates have reached nearly 95 and 85 percent, respectively, in many reputable transplant centers. However, the survival rates are not as favorable for people who have hepatitis C caused by recurrent liver disease from reinfection of the liver by the virus.

The improvement in outcomes and better awareness have resulted in an increasing demand for liver transplants in the United States during the past 20 years. Approximately 40 percent of transplantations done in the United States are for hepatitis C–related liver disease or cancer. The increased demand for healthy livers has exceeded the supply, resulting in longer waiting periods and higher death rates for people on the waiting lists. Each year, approximately 10 to 20 percent of people on liver transplant waiting lists die before receiving an organ. Transplant physicians have responded to this increased demand by developing

several different strategies for identifying potential donors, including the use of

- Organs from older donors
- Grafts from donors who have a "healthy" liver but are positive for hepatitis C or previous hepatitis B infection
- Grafts from non-heart-beating donors (usually a liver is taken only from donors whose heart is beating but whose brain is dead)
- Domino transplantation (in which liver from donors who have familial amyloid polyneuropathy is transplanted into older recipients, because these donors have relatively normal livers and their disease is a result of their liver producing an abnormal protein; the disease appears only after many years of exposure to this abnormal protein)
- Split-liver grafts
- Live donor liver transplants

Currently, there is an enormous disparity in supply and demand for liver grafts in the United States. Therefore, it has become necessary for the transplant community to ration the available organs in a way that serves the best interests of the population as a whole. This chapter discusses the process of selecting individuals for liver transplantation (criteria applicable to all people) and the expected outcomes for individuals who have hepatitis C–related cirrhosis or those who have a small liver cancer, which is a well-known complication of cirrhosis.

When evaluating a potential candidate for transplantation, physicians must assess whether the recipient is going to benefit from the procedure, both immediately and in the long term. The physician will examine the cause of liver disease, stage of disease, and estimated survival rates, as well as weigh the benefits and limitations of having the transplant versus not having the transplant.

For example, a person who has mild alcoholic cirrhosis without any major complications may have a comparable five-year survival with or without transplantation. Considering the long-term complications from

immunosuppressive drugs, the huge costs, and the relatively high immediate risk of death from surgery, this person may benefit more from conservative treatment and having a liver transplant at a later date if progressive disease develops. Similarly, a person who does not have cirrhosis and has primary sclerosing cholangitis, a condition in which the bile ducts inside and outside the liver are damaged, may ask for a liver transplant because of fear about developing cancer. Although this person's lifetime risk of developing cancer is approximately 15 percent, the risk of death associated with liver transplantation in the first five years is approximately 20 percent. This person should be advised about the expected outcome and discouraged from early transplantation, waiting until serious complications develop or until prediction models such as the Mayo model score, or model for end-stage liver disease (MELD) score, suggest that the person's life expectancy is less than two years without transplantation.

Although risk of death is an important consideration, the quality of life is equally important. People who may not fulfill all the criteria for transplantation may receive organ transplants because of chronic itching, fatigue, repeated bouts of cholangitis, or hepatic encephalopathy. The process of selecting and evaluating potential liver transplant recipients, the evaluation of such recipients, and the issues surrounding liver transplant waiting lists are discussed in this chapter.

Organ Recipient Evaluation Process

When evaluating individuals for liver transplantation, the transplant team does not have a set of rigid criteria or guidelines, but they try to make the best decision for the individual and society. A multidisciplinary team, consisting of a hepatologist, surgeon, social worker, psychologist, and transplant coordinator, discusses the best options and uses data from published studies and experience to decide. The rationale for making these decisions is clearly documented and conveyed to the referring physician or potential recipient as soon as possible.

Questions Used To Evaluate a Person for Possible Liver Transplantation

1. Does the person suffer from a disease that will benefit from liver transplantation? If so, how soon does that person require a liver transplant? Is the disease sufficiently advanced to meet the minimal listing criteria for liver transplantation?
2. Does the person have any other diseases or conditions that would prohibit an acceptable outcome of liver transplantation?
3. Is there a social system that will allow adequate follow-up after transplantation and a support mechanism that will take care of the person if the person develops serious complications? Is there a past or current history of alcohol or drug use? If there is, what are the chances of recidivism?
4. Finally, would the person benefit from expedited live donor liver transplantation?

The process of answering these questions is discussed in more detail in the following sections.

Reasons for and Urgency of Transplantation

Does the person suffer from a disease that will benefit from liver transplantation? If so, how soon does that person require a liver transplant? Is the disease sufficiently advanced to meet the minimal listing criteria for liver transplantation?

Liver disease and liver failure and, specifically, cirrhosis from any cause are potential reasons for liver transplantation (table 17.1). The following conditions are indications for liver transplant:

- Hepatitis C
- Alcohol abuse
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Budd-Chiari syndrome

- Wilson's disease
- Alpha-1-antitrypsin deficiency
- Polycystic liver disease
- Glycogen storage disease
- Familial amyloid polyneuropathy
- Hereditary oxalosis

The presence of cirrhosis alone does not warrant immediate evaluation or transplantation. Approximately 70 percent of individuals who have hepatitis C–induced cirrhosis live 10 years or longer without any cirrhosis-related complications. However, when people start having complications, the prognosis becomes poor. Approximately 70 percent of people will require a liver transplant within 10 years after they develop complications.

To be added to the transplant list, people should have sufficient evidence to warrant a transplant based on their history, their clinical or biochemical (blood tests) evaluation, and a life expectancy likely to be less than two years without transplantation.

Table 17.1. Reasons for Liver Transplantation

Fluid in the abdomen (ascites) that does not respond to sodium restriction and diuretics
Infection of fluid in the abdomen (spontaneous bacterial peritonitis)
Confusion (hepatic encephalopathy)
Yellow discoloration of the eyes (persistent jaundice)
Presence of a small liver cancer
Kidney failure caused by liver disease (hepatorenal syndrome)
Bleeding from the stomach or esophagus despite transjugular intrahepatic portosystemic shunt (TIPS)
Child C cirrhosis (unlikely to improve with treatment or with abstinence from alcohol or medications)
High MELD score (20 or more)

Table 17.2. Characteristics Contributing Points to the Child-Pugh Score

Characteristic	*1 Point*	*2 Points*	*3 Points*
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4
Fluid in abdomen (ascites)	None	Slight (or controlled by diuretic)	At least moderate (despite diuretic)
Bilirubin (mg/dl)	<2	2 to 3	>3
Albumin (g/dl)	>3.5	2.8 to 3.5	<2.8
International normalized ratio (INR)	<1.7	1.7 to 2.3	>2.3

Child-Pugh Score

The Child-Pugh score classifies the severity of chronic liver disease. Scores are based on a summation of points (table 17.2): Child A, 5 to 6 points; Child B, 7 to 9 points; Child C, 10 to 15 points.

Model for End-Stage Liver Disease (MELD) and Organ Allocation

The model for end-stage liver disease (MELD) score was developed by a group of physicians at the Mayo Clinic and predicts risk of death for people who have severe liver disease. Currently, a modified version of this model used by UNOS helps prioritize organ allocation for people on the transplant waiting list.

The MELD score is calculated on the basis of serum bilirubin, international normalized ratio (INR), and serum creatinine, using the following formula:

$$\text{MELD score} = 3.8 \times \log_e (\text{bilirubin [mg/dl]}) + 11.2 \times \log_e (\text{INR}) + 9.6 \times \log_e (\text{creatinine [mg/dl]}) + 6.4$$

The MELD score ranges from 6 to 40, and because individuals who have higher scores are more likely to die without a liver transplant, they are given priority.

The organs are allocated on a local and regional basis. The United States is divided into 11 regions, and each region is further subdivided

based on local organ procurement organizations, of which there are 58 in the United States. The components of each region are as follows:

Region 1: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont
Region 2: Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia
Region 3: Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico
Region 4: Oklahoma, Texas
Region 5: Arizona, California, Nevada, New Mexico, Utah
Region 6: Alaska, Hawaii, Idaho, Montana, Oregon, Washington
Region 7: Illinois, Minnesota, North Dakota, South Dakota, Wisconsin
Region 8: Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming
Region 9: New York, Western Vermont
Region 10: Indiana, Michigan, Ohio
Region 11: Kentucky, North Carolina, South Carolina, Tennessee, Southern Virginia

Organs are allocated in descending order of MELD score (person with highest MELD score first, followed by the next highest, and so on), stratified by the person's blood type.

People who have liver cancer and fall within the Milan criteria get arbitrary MELD scores (usually starting at 22 points) and additional points (usually 3 points) every three months until they receive a transplant or are removed from the list. The MELD scores for individuals who have liver cancer are not calculated as for other people unless the liver disease is advanced in those with liver cancer and the calculated MELD score is higher than the arbitrary score assigned to them. People receiving dialysis are arbitrarily assigned a creatinine level of 4 mg/dl when calculating their MELD score.

The organ allocation policy may continue to be modified; to view the most recent policy, visit the U.S. Health Resources and Services

Administration Organ Procurement and Transplantation Network website (http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf).

For children, the severity of liver disease is assessed using the pediatric end-stage liver disease (PELD) score and is not discussed in detail here. The PELD score is calculated on the basis of serum albumin, bilirubin, INR, age, and the presence or absence of growth failure.

Adult Donor Liver Allocation Algorithm

A donor liver is allocated (this does not apply to live donors) on a local, regional, or national basis. Because of the seriousness and sensitivity of organ allocation, UNOS has carefully drafted the policy to ensure that the sickest person receives a liver transplant. Usually, the organ procurement organization allocates the organ to the local area first, but for people who have more severe disease, there is regional sharing. The sharing process (prioritization) at the local and regional levels is as follows:

Combined Local and Regional

Priority 1: Status 1A candidates in descending MELD score order.

Priority 2: Status 1B candidates in descending MELD score order.

First priority is to status 1A people. Status 1A is given to individuals (adults and children) who have acute liver failure and people who had failure of a transplanted liver immediately after the transplant (known as primary graft nonfunction). Status 1B is given to children who have chronic liver disease and have life-threatening complications.

Local and Regional

Priority 3: Candidates who have MELD/PELD scores of 35 or more in descending MELD score order, and local candidates ranked above regional candidates at each level of MELD score.

Local

Priority 4: Candidates who have MELD/PELD scores of 29 to 34 in descending MELD/PELD score order.

National

Priority 5: Candidates waiting for both liver and intestine in descending MELD score order.

Local

Priority 6: Candidates who have MELD/PELD scores of 15 to 28 in descending MELD score order.

Regional

Priority 7: Candidates who have MELD/PELD scores of 15 to 34 in descending MELD score order.

National

Priority 8: Status 1A in descending MELD score order.

Priority 9: Status 1B in descending MELD score order.

Priority 10: People who have MELD/PELD scores of 15 or more in descending MELD score order.

MELD scores are periodically reassessed and recertified by the listing transplant center. The frequency of recalculation is based on the MELD score. People who have lower MELD score are less likely to receive a liver transplant, and therefore their score is not recalculated frequently. For people who have more severe liver disease, scores are recalculated and recertified more frequently.

Intervals for Recalculation and Recertification of MELD Score While on the Transplant List

For status 1 and people who have a MELD score of more than 25, laboratory tests should be done within 48 hours of recertification. The scores should be calculated based on the most recent blood tests within the time period shown in table 17.3.

The decision to list a person for a transplant does not indicate that the person is in need of immediate transplantation. However, it is prudent not to list someone if that person will require a liver transplant in the next two to three years, as waiting time is no longer important for liver transplantation. Once listed, the person is reassessed periodically by the physician to assess disease progression and MELD score. A person who

Table 17.3. Intervals for Recalculation and Recertification with the United Network for Organ Sharing for the Transplant Waiting List

Points	*Intervals*
Status 1	7 days (blood tests should be done within 48 hours)
More than 25	7 days (blood tests should be done within 48 hours)
19 to 24	30 days (blood tests should be done within 7 days)
11 to 18	3 months (blood tests should be done within 14 days)
Less than 10	1 year (blood tests should be done within 30 days)
Liver cancer	MELD recalculated every 3 months

is on the list and has a stable course or has improved since listing may be removed from the list.

The selection criteria for liver transplantation for people who have evidence of liver cancer are discussed later in this chapter. These individuals are given additional MELD points as described above.

Co-morbid Conditions

Does the person have any other diseases or conditions that would prohibit an acceptable outcome of liver transplantation?

One of the important functions of the selection process is to assess whether the potential recipient can withstand a transplant operation and emerge with an acceptable quality of life. If the person's risk of death associated with transplantation outweighs that of the severity of the liver disease, then a transplant is not in the person's best interest (table 17.4). To assess the chances for a successful outcome, the physician will ask the person for detailed information relating to any other medical conditions, including diabetes, heart-related risk factors, kidney disease, and cancer. Although most centers do not have an absolute age cut-off, people older than 65 years are considered on an individual basis, depending on their general condition and the presence of other diseases.

Although the risk factors listed in table 17.4 increase the risk of immediate death and decrease long-term survival after liver transplantation, these risk factors need not preclude someone from receiving a liver

Table 17.4. Risk Factors That Predict a Poor Outcome after Liver Transplantation

Age older than 70 years
Uncontrolled diabetes with diabetes-related complications, such as generalized vascular disease
Severe obesity (body mass index more than 40)
Coronary heart disease
Kidney failure
Transplantation while in the intensive care unit
MELD score more than 35

transplant. People who have established kidney failure may need both liver and kidney transplantation. A person's age has less effect on the immediate outcome and a more negative effect with long-term survival, which may be related to the confounding influence of other diseases. People who have diabetes or coronary heart disease are approximately 40 percent more likely to die within five years after transplantation than people who do not have diabetes or heart disease. Individuals who have risk factors will be assessed by their physician with appropriate tests and treated as necessary before liver transplantation.

Support System and History of Drug or Alcohol Use

Is there a social system that will allow adequate follow-up after transplantation and a support mechanism that will take care of the person if the person develops serious complications? Is there a past or current history of alcohol or drug use? If there is, what are the chances of recidivism?

Often, the most difficult and challenging issue that the transplant committee has to manage is whether appropriate social support exists for a potential recipient. Many people who have hepatitis C–related cirrhosis lack a nurturing environment to care for them after the transplantation procedure. Failure to follow up with laboratory examinations and appointments, as well as missed medications, can have extremely deleterious effects on liver transplant recipients, leading to organ rejection and late diagnosis of associated complications. To address this aspect,

potential recipients undergo an evaluation by a social worker and psychologist dedicated to the transplant program, to allow the most educated decision possible. After their evaluation, the entire transplant team discusses the candidate's circumstances before making a decision.

Abstinence from drugs and alcohol is a prerequisite for being listed for a liver transplant. At most institutions, people who are addicted to alcohol and drugs need to complete a preapproved outpatient alcohol or drug rehabilitation program, with documented abstinence for at least six months before being considered for transplantation. People who are found to be using drugs or alcohol while they are on the transplant list are removed from the list. It is preferable for transplant programs to have rigid, written criteria regarding alcohol and substance abuse—agreed upon by the members of the transplant team—to ensure objective decisions, because bias, culture, and preconceived beliefs may lead to unfair decisions.

Live Donor Liver Transplantation

Would the person benefit from expedited live donor liver transplantation?

The advantages of live donor liver transplantation include

- Selective and expedited transplantation for people who have advanced cirrhosis
- Ability to optimize the recipient's health status, elective surgery, and decrease in cold-ischemia time (the amount of time the liver is without blood flow; this starts when the organ is chilled with a cold perfusion solution and ends when the organ reaches normal physiological temperature after being transplanted into the recipient)
- Increase in number of potential organ donors (increase in the number of transplantations)

The major disadvantage of live donor liver transplantation is the potential risk of illness and, in some cases, risk of death for the donor. The concept of performing a major operation that has a potential risk of death

for a healthy person (the donor), without any direct benefits to that person other than psychological, is unique. Unlike live donor kidney transplantation, donation of a liver (usually the right lobe or 60 to 65 percent of the liver) to another adult is associated with significant donor illness and a risk of death of about 0.5 percent.

Expedited transplantation is of particular benefit for people whose need for transplantation may not be accurately reflected by their MELD score, such as people who have complications of portal hypertension (refractory ascites, spontaneous bacterial peritonitis, or encephalopathy) and have a relatively low MELD score. These are the ideal candidates for live donor liver transplantation, and they should be allowed to pursue this option if they have suitable family members or friends who are willing to donate part of their liver. Although highly controversial, people who have liver cancer that is inoperable and do not fulfill the current criteria for higher MELD score (tumor larger than 5 cm in diameter or more than three lesions) may also be considered for live donor liver transplantation, with an understanding that they will not be given cadaver organs if the live donor liver transplantation fails.

The American Society of Transplant Surgeons' position paper on adult-to-adult living donor transplantation suggested that recipients should be medically suitable for transplantation by the standard criteria of the institution and should understand and accept that the donor will be put at significant risk. The paper also recommended that the risk to the donor should be weighed against the realistic estimate of a successful outcome, and this is an important consideration when live donor liver transplantation is offered to recipients who are expected to have a poor outcome with a cadaver liver transplant. People who have hepatitis C are offered live donor liver transplantation on the basis of medical necessity, not on the basis of donor availability. Clearly, the benefits should outweigh the immediate risks of surgery to the recipient and, more importantly, to the donor.

To be eligible to receive an organ from a live donor, a person should meet all the criteria necessary to be listed for a cadaver organ, which allows for retransplantation with a cadaver liver if the live donor liver transplantation fails. This process will confirm the medical necessity for

liver transplantation. In addition, the need for live donor liver transplantation is discussed by the multidisciplinary transplant committee. When people become critically ill, live donor liver transplantation may have a poor outcome, and these people may have a more successful outcome with cadaver transplantation. It has been shown that people who receive organ transplants and have advanced cirrhosis may require a larger amount of donor liver than recipients who have more stable disease. However, this criterion is not to be used as a justification for early live donor liver transplantation, because many people may be able to wait to receive a cadaver transplant in a timely fashion. Donor safety is of paramount importance in live donor liver transplantation. Therefore, this procedure is not recommended to recipients whose predicted postoperative survival is poor based on their pretransplant health status.

Many studies show that short-term individual survival after live donor liver transplantation is comparable to that of cadaver transplantation. However, the concern for donor safety and lower graft survival remain the critical issues. Most donors are satisfied with the process of live donor liver transplantation, and when donors are interviewed, they express a willingness to accept significant risks (including an increased risk of death) to save a family member or friend. However, this unrealistic tolerance for adverse donor outcomes is not shared by the medical community. The optimistic attitude of potential donors is a clear signal to the medical community of the need to improve outcomes and continue live donor liver transplantation. It also reinforces the importance of having a multidisciplinary team approach, with objective criteria for the selection of donors and recipients for adult live donor liver transplantation.

Pretransplant Evaluation

If a person has been selected for a liver transplant, and if no obvious contraindications are identified on the initial clinical visit, potential recipients, whether for live donor or cadaver transplantation, undergo a comprehensive evaluation by the transplant team. The evaluation includes the following tests:

- Lung function tests
- Electrocardiogram
- Chest X-ray
- Echocardiogram
- Routine blood tests
- Tests for HIV, hepatitis B, cytomegalovirus, and syphilis
- Dobutamine stress echocardiogram or thallium scan for people older than 50 years or people who have a history of diabetes or hypertension or a family history of cardiac disease
- Coronary arteriogram and carotid duplex, if the physician suspects the person has coronary heart disease
- Three-dimensional CT scan or magnetic resonance imaging to evaluate the hepatic vascular anatomy

In addition, potential recipients are interviewed by members of the transplant team, including the hepatologist, transplant surgeon, social worker, psychologist, and transplant coordinator. Further consultation (cardiology, pulmonary, oncology, etc.) is requested depending on the initial evaluation. The multidisciplinary transplant team members discuss the results and decide upon the suitability of the recipient for liver transplantation. If necessary, the team may request further evaluation or tests before making a final decision.

Liver Cancer (Hepatocellular Carcinoma or Hepatoma)

Almost all people who have hepatitis C have cirrhosis when they develop liver cancer. People with hepatitis C cirrhosis have a 3 to 4 percent risk every year for developing liver cancer. The cumulative risk of developing liver cancer in hepatitis C cirrhosis is high, especially for people who had previous alcoholism. People who have untreated liver cancer have a dismal prognosis, with a median life expectancy of six to nine months. Less than 20 percent of people who have liver cancer are potential candidates for surgical removal of the tumor. The remaining 80 percent cannot have surgery because of the size and location of the tumor or the severity of underlying liver disease.

Table 17.5. Milan Criteria for Assessing Liver Cancer

If only one tumor, it should be less than 5 cm in maximum diameter
or
If more than one tumor, each tumor should be less than 3 cm, with no more than three tumors
and
No major blood vessel involvement or spread outside the liver

For people who have cirrhosis and do not have liver cancer that has spread to other parts of the body, liver transplantation probably offers the best chance of long-term survival because it treats the cancer as well as the underlying liver disease. Recent reports show an excellent outcome for carefully selected people who have liver cancer. The size of the tumor (smaller than 5 cm if single, smaller than 3 cm if more than one and fewer than three), number of nodules (fewer than three), and absence of blood vessel involvement (collectively called the Milan criteria; table 17.5), and a well-differentiated tumor (as evaluated by biopsy), are associated with better posttransplant survival.

Although use of the Milan criteria is not mandatory, most centers have adopted these criteria for recipient selection over the past decade. Additionally, extra MELD points (for expedited liver transplantation) are given only to people who fulfill the Milan criteria. In addition to routine tests, people who have liver cancer undergo chest CT scans and bone scans to assess whether the cancer has spread.

Shortage of donor organs and the long waiting period, allowing progression of both the tumor and the underlying liver disease, are two major limiting factors for transplantation for people who have liver cancer. The transplant community has recognized that liver transplantation, if done expeditiously, is the optimal treatment for liver cancer and advanced cirrhosis. Therefore, in 2002, when UNOS adopted the MELD scoring system to prioritize organ allocation, they decided to give arbitrarily chosen high MELD scores to people who fulfill certain criteria (similar to the Milan criteria) to expedite their transplantation procedure. Live donor liver transplantation is another option for people who have liver cancer.

Results of Liver Transplantation for Hepatitis C

About one-third of liver transplantations done in the United States are for cirrhosis related to hepatitis C infection. Recurrent hepatitis C infection is universal in people who have an active hepatitis C infection (presence of hepatitis C RNA detected by polymerase chain reaction testing) at the time of liver transplantation. Recurrent hepatitis C virus in the blood usually develops within days after transplantation. Although recurrent disease is often mild initially, approximately 10 to 20 percent of individuals develop cirrhosis within two years. Rarely (less than 1 in 1,000 people), an aggressive form of hepatitis C infection (fibrosing cholestatic hepatitis) may cause liver failure after transplantation within weeks or months. Several related factors regarding the virus and the individual have been proposed to explain the different outcomes, including hepatitis C viral load, virus genotype, and organ rejection episodes, as well as suppression of the person's immune system.

Although the 1-year survival rate is favorable (approximately 85 to 90 percent) for people who have hepatitis C, the 5-year survival rate is 70 percent and the 10-year survival may be lower than 60 percent. The relatively low survival rate for people who have hepatitis C is due to recurrent disease that often progresses to cirrhosis.

Until recently, the treatment of hepatitis C infection after a liver transplant was not very effective. Suppression of a person's immune system to allow acceptance of the transplanted organ enables the virus to multiply more aggressively, making the person less susceptible to treatment with interferon and ribavirin. The rate of sustained viral clearance in transplant recipients was low (less than 20 percent) with interferon and ribavirin. In addition, many transplant recipients do not tolerate treatment with interferon and ribavirin; also, interferon may potentially cause organ rejection, and ribavirin may cause severe anemia (because of kidney disease or damage).

There is encouraging evidence to suggest that transplant recipients could be treated more effectively with direct-acting antiviral medications, such as sofosbuvir in combination with ledipasvir and ribavirin (Harvoni with ribavirin) or the AbbVie regimen, as discussed in chapter 16.

Posttransplant Management

Transplantation is associated with many short-term and long-term complications, many of which are preventable with a better team approach and with better compliance from the organ recipient. The criteria for a successful outcome and fewer complications are summarized in table 17.6.

After liver transplantation, most people can lead a normal life. However, individuals who have received a transplanted organ should be aware of and avoid certain things that may increase the risk of complications and infections, including the following:

- In the immediate postoperative period, avoid going to crowded places, being near individuals who have viral infections, eating uncooked shellfish, and gardening.
- Avoid contact with people who have recently had live virus vaccines (for example, oral polio vaccine).
- Avoid getting vaccinated with live attenuated viruses or bacteria (live vaccines are made with a version of the virus or bacteria that is made weak in the laboratory, and these can potentially cause infection in an immunosuppressed person). Examples include oral polio vaccine and vaccines for mumps, measles, chicken pox, and herpes zoster; nasal spray for seasonal flu (injectable flu vaccine is not a live vaccine); and vaccines for rotavirus, adenovirus, and yellow fever. Bacterial vaccines such as that for typhoid are also live vaccines.
- Avoid heavy lifting in the first few months, and then begin a graded exercise program.
- Avoid alcohol.
- Do not take any new medications, even if only for a short time, before checking with your physician or pharmacist, because there may be drug interactions.
- Consult with a transplant physician before switching the immunosuppressive regimen.

After liver transplantation, individuals should have regular blood tests to monitor liver enzymes, blood levels of immunosuppressants (for ex-

Table 17.6. How Organ Recipients Can Improve Liver Transplantation Outcomes

Be well informed about liver transplantation, including its risks and complications.
Follow the transplant team's instructions. Because the team manages many liver transplant cases, team members are likely to be a better source of information than many websites or other people's experiences. Major concerns regarding management should be discussed with a transplant physician.
Have blood tests done periodically as recommended by the transplant team (see table 17.7). Follow up on blood test results, and make sure the team has seen the results. If possible, obtain a copy for your medical records. Learn what the blood tests mean. Call the transplant physician if there is a major change in blood test results or you have any new symptoms. Sometimes the physician may not have received or seen the test results.
Take medications as recommended. Do not miss any doses, and do not self-treat.
Maintain your health and manage any other health conditions. Optimal health maintenance is essential for a better outcome. The long-term outcome depends on better management of other conditions or drug-related complications, such as diabetes, hypertension, obesity, high cholesterol, kidney failure, and cancers. Few people die from liver disease after the immediate postoperative period.

Table 17.7. How Often Should a Liver Transplant Recipient Get Blood Tests?

Time after Transplantation	*How Often?*
0 to 3 months	1 to 2 times per week
3 to 6 months	Every 1 to 2 weeks
6 to 12 months	Every 2 to 4 weeks
1 to 5 years	Every 4 to 6 weeks
After 5 years	Every 3 months

Common blood tests include complete blood count (hemoglobin, white blood cells, platelets), comprehensive profile (blood sugar, creatinine, electrolytes), magnesium level, and immunosuppressive drug (tacrolimus, cyclosporine, or sirolimus) level.

ample, tacrolimus), and kidney function. Blood tests are done more frequently immediately after transplantation, and the interval between tests increases with time (table 17.7). Blood tests are also done more frequently if there is a suspicion of rejection or other complications.

Complications

Immediate Complications

Because the surgical team closely monitors all liver transplant recipients, the immediate complications of liver transplantation are managed well. Immediate complications are mostly caused by surgical complications and bacterial infections (table 17.8). After two to four weeks, opportunistic viral infections—cytomegalovirus is the most common—may occur, and people who are at risk of cytomegalovirus infection will be given prophylactic treatment with an antiviral medication called ganciclovir. To prevent yeast infection and *Pneumocystis carinii* infection, individuals are treated in the first six months after transplantation with fluconazole and Bactrim. These prophylactic drugs are discontinued after six months.

Table 17.8. Immediate Complications of Liver Transplantation

Complications	*Outcome*
Complications from surgery	Blood loss is common and may require many units of blood or blood products.
	Blockage of an artery in the lungs is extremely rare.
	Blockage of a liver artery may require another surgery or radiological intervention (less than 2% to 3%).
	Liver graft that is not working (less than 5%) usually requires retransplantation.
	Bile leak (up to 10%) is easily managed with a stent.
Potential infections	Bacterial infections (chest, urinary tract, abdominal cavity, and wound) in the first few days.
	Viral infection (opportunistic infections such as cytomegalovirus) after the first 2 to 3 weeks.
	Fungal (yeast) infections in the immediate postoperative period.
Organ rejection	Minor rejection (~20% to 40%) is easily treated with medications, including steroids and, rarely, monoclonal antibody.
Death	Occurs in less than 5% of transplant recipients.

Late Complications

Transplant recipients may opt not to follow up with physicians who have experience with liver transplantation. In general, people who are well informed do better than individuals who leave their management to their treating physician, who may not be an expert in the field of liver transplantation. It may be useful to continue the follow-up at a transplant center (if possible). If that is not possible, people should try to periodically communicate with the transplant team by telephone. Communications by letter are often not appropriate because the transplant team is usually busy with many unexpected issues, and letters are less likely to receive early attention. If people do not hear back, they should continue to call until they reach a transplant team physician.

Late complications are described in table 17.9. A significant number of complications are related to drugs that suppress the immune system or aggravate preexisting conditions. Obesity is a major problem after liver transplantation, as are high blood pressure and diabetes. These conditions, along with drugs such as tacrolimus and cyclosporine, cause accelerated clogging of the arteries; people should control obesity, diabetes, high blood pressure, and high cholesterol aggressively after liver transplantation.

Skin cancers (basal and squamous cell) are more common in people who have received a transplant, and individuals should see a dermatologist if they have any skin lesions. It is recommended that organ recipients see a dermatologist once a year for a routine examination. Because individuals who receive transplants are immunosuppressed, they are also at increased risk of developing other cancers, such as lymphoma and cancer of the breast, prostate, or colon. People who have inflammatory bowel disease should undergo a yearly colonoscopy to screen for colon cancer. People should also maintain a healthy lifestyle and diligently manage any conditions to prolong their life expectancy after liver transplantation.

Table 17.9. Late Complications of Liver Transplantation

Complications	*Outcome*
Hypertension	Common (20% to 30%) and may be related to tacrolimus or cyclosporine.
Diabetes	May be related to tacrolimus or cyclosporine (10% to 15%).
Kidney failure	At 5 years, up to 20% develop kidney failure, probably because of tacrolimus, cyclosporine, diabetes, or hypertension.
High cholesterol	May be related to medications, obesity, or diabetes. Sirolimus is known to cause high cholesterol.
Anemia	Common (30% to 40%). May be multifactorial and is usually mild.
Osteoporosis	Common, especially with steroid use.
Cancers	Skin cancers are common. Other cancers include breast, colon, and prostate cancer.
Lymphoproliferative disease	May be related to Epstein-Barr virus (the same virus that causes infectious mononucleosis); seen in less than 3% of transplant recipients.
Obesity	Most common problem.
Bile duct problem	In up to 10% of transplant recipients.
Recurrent disease	Depends on the primary disease.

Immunosuppressive Medications

The common drugs used to suppress the immune system after transplantation are listed in table 17.10. Although these drugs are life-saving, they are associated with many side effects. By maintaining appropriate blood levels, the side effects can be minimized. Renal failure is a major problem after liver transplantation, especially in long-term survivors. Medications with less renal toxicity (such as sirolimus) should be considered for people who have renal impairment.

In 2013, everolimus (similar to sirolimus) was approved by the Food and Drug Administration to be used in combination with either tacrolimus or cyclosporine.

Table 17.10. Common Immunosuppressive Agents Taken after Liver Transplantation

Agent	*Properties*
Tacrolimus (Prograf), twice daily	Commonly used inhibitor of calcineurin (an enzyme that activates T cells). Blood levels should be maintained between 6 and 12 ng/ml (trough levels before taking the medicine in the morning), depending on the interval after transplantation and other immunosuppressive medications used.
Cyclosporine (generic and Neoral), twice daily	Commonly used calcineurin inhibitor. Blood levels should be maintained between 100 and 200 ng/ml (trough levels before taking the medicine in the morning), depending on the interval after transplantation and other immunosuppressive medications used.
Sirolimus, once daily	Relatively new drug. Approved for kidney transplantation. No kidney toxicity. Blood levels between 6 and 10 ng/ml.
Mycophenolate mofetil (Cellcept or Myfortic)	Used with tacrolimus, cyclosporine, or steroids. As a single agent, it is inadequate for immunosuppression and is used in combination with other drugs. Blood levels are not monitored.
Prednisone	Used only in the first few weeks; most people are weaned off the drug by 6 months. Used with other drugs in the immediate postoperative period.

Many possible drug interactions can occur, and some of the commonly used antibiotics can either increase or decrease blood levels of immunosuppressive medications; therefore, it is important to consult with the physician before starting any new medications, including antibiotics. If a physician is not available, ask a pharmacist whether there are any potential drug interactions.

Liver transplantation is a life-saving procedure, but given the limited supply of organs, novel approaches are required for increasing the number of potential donors. To increase the success of transplantation and long-term survival rates, a team of professionals evaluates and selects people for liver transplantation based on medical, psychological, and social factors.

Individuals who receive a liver transplant need life-long follow-up, but they can expect an excellent quality of life. New treatment options are now available for people who have received liver transplants for hepatitis C infection to prevent recurrence of hepatitis C.

The field of liver transplantation is dynamic, and, as new technologies become available, the liver transplantation process will continue to evolve.

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Recurrence of Hepatitis C after Liver Transplantation

Hepatitis C virus–related liver disease (decompensated, or worsening, cirrhosis or liver cancer) is the most common indication for liver transplantation. Recurrence of hepatitis C infection occurs in all people who are positive for hepatitis C RNA at the time of transplantation. The disease may progress rapidly in some transplant recipients.

- Recurrence of hepatitis C is universal after liver transplantation if the recipient is hepatitis C RNA-positive at the time of transplantation.
- Approximately 30 percent of individuals may develop cirrhosis within five years from the time of transplantation.
- Once cirrhosis develops, complications such as ascites and encephalopathy follow rapidly.
- Early recognition of progressive disease and treatment of hepatitis C will improve long-term survival.

Several studies show that the progression of scar formation (fibrosis) is accelerated in transplant recipients compared with people who have hepatitis C and have not received an organ transplant. The early recognition of progressive, recurrent hepatitis C in transplant recipients will improve survival and reduce complications.

Curing hepatitis C before transplantation, even in the presence of advanced cirrhosis, may become possible in the near future with interferon-free medications. Moreover, with newer medications, the cure of hepatitis

C after liver transplantation—without serious complications, including rejection—may become possible.

Progression of Recurrent Hepatitis C after Transplantation

The five-year survival rate after transplantation for hepatitis C is 61 to 75 percent, compared with 76 to 85 percent for other causes of liver disease, including hepatitis B. The predominant reason for the lower survival rate of people who have hepatitis C infection is recurrence of cirrhosis. Because people who have received organ transplants have weakened immune systems, fibrosis progresses at an accelerated rate, resulting in cirrhosis in 30 percent of transplant recipients within five years after transplantation. Of these, 30 percent have deteriorating liver function (hepatic decompensation) within one year after development of the cirrhosis. In less than 1 percent of people, fibrosing cholestatic hepatitis, an uncommon and aggressive form of recurrent hepatitis C, leads to rapid liver failure and graft loss.

> Five-year survival rate after liver transplantation in people who have hepatitis C is 61 to 75 percent, compared with 76 to 85 percent for people receiving transplants for reasons other than hepatitis C.

Reasons for Rapid Progression

There are several reasons for the rapid progression of hepatitis C in transplant recipients, including donor and recipient characteristics and immunosuppression. Table 18.1 shows important factors that lead to rapid progression, but it is difficult to predict the prognosis for an individual before or immediately after transplantation. Advanced donor age and aggressive immunosuppressive treatment are two major factors that lead to severe recurrence and rapid progression.

Table 18.1. Risk Factors for Rapid Progression of Recurrent Hepatitis C after Liver Transplantation

Donor characteristics:
Advanced age
Moderate or severe fat content in the donor graft
Prolonged cold-ischemia time
Donor non-CC IL28B genetic mutation
Recipient characteristics:
Advanced age
HIV and hepatitis C co-infection
Cytomegalovirus infection after transplantation
Diabetes mellitus
Immunosuppression
High steroid dose, especially when treated for rejection
Very potent immunosuppressive agents (OKT3, ATG, alemtuzumab)

Assessment of Progressive Disease

Recurrence of liver disease due to hepatitis C infection is confirmed when liver enzymes are elevated and the liver biopsy shows features of viral hepatitis (table 18.2).

Fibrosis rate is accelerated in most people who have hepatitis C, with 20 to 54 percent developing advanced fibrosis or cirrhosis within the first five years after transplantation. The correlation between liver enzymes and histology is poor, and liver biopsy is the only way to assess the severity of fibrosis (table 18.3).

Measurement of the hepatic venous wedge pressure gradient (HVWPG) during transjugular liver biopsies can enhance diagnostic accuracy, especially in identifying people at high risk of hepatic decompensation, but the procedure is very invasive. Ultrasound-based transient elastography (using FibroScan) is a promising noninvasive test for the detection of liver fibrosis through the measurement of liver stiffness (measured in kilopascals, kPa). This method may replace liver biopsy in the future for ongoing assessment of fibrosis, but its major limitation is the inability to discriminate intermediate stages of fibrosis; moreover, it is not applicable for many obese people.

Table 18.2. Diagnosis of Recurrence of Liver Disease from Hepatitis C Infection after Transplantation

Elevated liver enzymes
Presence of HCV RNA in the blood
Liver biopsy showing features of viral hepatitis

Table 18.3. Monitoring the Severity of Fibrosis after Transplantation

Yearly protocol liver biopsy is probably the best strategy.
Alternative option is serial measurement of liver stiffness with FibroScan (not studied well).
Another option is measurement of hepatic venous wedge pressure gradient (HVWPG), but this is very invasive and not often used.
Antiviral treatment is considered when fibrosis progresses rapidly (stage 2 or more), but this may change when the safety of direct-acting antiviral drugs in liver transplant recipients is established.

Several serum biomarkers and their combinations have also been studied for assessing the severity of fibrosis. These biomarkers are considered experimental at this stage, and more studies are required before applying this method in clinical practice. Because of the limited and inconsistent data with biomarkers and FibroScan, liver biopsy remains the optimal modality to assess fibrosis after liver transplantation.

Treatment of Hepatitis C in Liver Transplant Recipients

Curing hepatitis C before liver transplantation will eliminate the risk of hepatitis C recurrence. However, interferon-based treatment is not applicable for people who have advanced liver disease, because of poor tolerance, severe anemia, neutropenia (low white blood cells) and thrombocytopenia (low platelets), decompensation of liver disease (ascites, encephalopathy), and life-threatening infections. Currently, there are no data on the use of direct-acting antiviral drugs for people who have advanced liver disease (with jaundice, ascites, encephalopathy, or Child C),

but many of these people could probably be cured with selected antiviral drugs. More clinical trials are necessary in this area.

Sofosbuvir in combination with ribavirin is approved by the Food and Drug Administration (for a maximum of 48 weeks or until liver transplantation, whichever comes first) for use in people with compensated (well-controlled) liver disease (Child A) and liver cancer who are awaiting a liver transplant. The idea behind this treatment regimen is to clear the virus before transplantation, thereby reducing the likelihood of recurrence. In one small study, 36 people who had liver cancer and, after 48 weeks of treatment, had undetectable hepatitis C virus in their blood underwent liver transplantation. Of these, 23 (64 percent) had no evidence of recurrence at 12 weeks after transplantation. Many of these people could tolerate more efficacious drug combinations, and it is unlikely that the sofosbuvir and ribavirin combination will be used for people who have liver cancer in the near future.

Another strategy is prophylactic or preemptive antiviral treatment in which treatment is initiated immediately after liver transplantation, before biopsy evidence of recurrence. This strategy was tested in one study and was found not to have any advantage in terms of efficacy. Currently, most liver transplant centers initiate treatment only when there is evidence of progressive disease, but this strategy may change when safer and more effective interferon-free antiviral treatments become available. The current strategy, summarized in table 18.4, is to treat individuals who, on liver biopsy, have stage 2 or more fibrosis or significant inflammation and when there is progressive disease on serial protocol biopsies.

Table 18.4. Indications for Hepatitis C Treatment after Liver Transplantation

Stage 2 or more fibrosis on liver biopsy
Severe inflammation on liver biopsy
Progression of fibrosis on serial protocol (usually yearly) liver biopsies
Aggressive recurrence such as fibrosing cholestatic hepatitis (presents with jaundice)

Expected Cure Rates for Hepatitis C Recurrence

In clinical studies, treatment with pegylated interferon and ribavirin cured only 20 to 30 percent of people who had genotype 1 infection. More importantly, many people had to discontinue treatment because of serious side effects. In hepatitis C genotypes other than genotype 1, the cure rates were higher (45 to 65 percent). (Cure rates are summarized in table 18.5.)

Higher cure rates were seen in genotype 1 infections (up to 40 percent) with a three-drug regimen using a protease inhibitor, telaprevir or boceprevir. An important limitation of these first-generation protease inhibitors is the drug-drug interactions with immunosuppressive agents. Both boceprevir and telaprevir are metabolized by the CYP3A system, and both increase the blood levels, severalfold (up to 100 times), of cyclosporine, tacrolimus, everolimus, and sirolimus. Dose adjustments and frequent monitoring of immunosuppressive levels are mandatory, especially during the first few weeks of initiation or discontinuation of these protease inhibitors. Moreover, both boceprevir and telaprevir are associated with significant adverse events, including anemia, skin rash (mainly with telaprevir), and fatigue, resulting in dose modifica-

Table 18.5. Reported Cure Rates for People Who Have Recurrent Hepatitis C

Treatment	*Cure Rate*
Pegylated interferon and ribavirin for 48 weeks	Genotype 1: 20% to 30% Genotypes 2 and 3: 45% to 65%
Pegylated interferon, ribavirin, and either telaprevir or boceprevir for 48 weeks	Genotype 1: ~40%
Sofosbuvir and ribavirin (limited data) for 24 weeks	Genotypes 1 and 3: ~70%
AbbVie regimen with ribavirin (limited data) for 24 weeks	Genotype 1: 97%
Ledipasvir-sofosbuvir (Harvoni) with ribavirin for 12 weeks	Genotype 1, including Child A cirrhosis: 96% Genotype 1, with Child B cirrhosis: 85% Genotype 1, with Child C: 60%

tions of ribavirin or interferon, as well as drug discontinuations. It is unlikely that either telaprevir or boceprevir will be used in the future, given the availability of safer, direct-acting antiviral drugs.

Interferon-Free Treatment

Non-interferon-based therapies with sofosbuvir or similar drugs may have great potential in the posttransplant setting, based on some studies. Fewer side effects and drug-drug interactions make these therapies more tolerable, and these drugs may result in higher cure rates. In one study, 40 people (34 with genotype 1 infection, 6 with genotype 3) who had recurrent hepatitis C (median time 4.3 years after liver transplantation) were treated with sofosbuvir and ribavirin for 24 weeks. Hepatitis C RNA became undetectable at week 4 in all participants, but 30 percent had disease relapse when treatment was discontinued. Nevertheless, 70 percent were cured with this treatment. These results are promising because treatment was discontinued as a result of side effects in only two people, and no one experienced graft rejection.

In another small study, all 34 people who completed 24 weeks of treatment with the AbbVie regimen (paritaprevir-ritonavir, ombitasvir, and dasabuvir) and ribavirin cleared the virus, and only one had disease relapse when treatment was discontinued. The cure rate with this treatment was 97 percent. The FDA has approved this regimen for recurrent hepatitis C infection, based on this clinical trial. The major disadvantage of the AbbVie regimen is drug-drug interactions. This regimen increases tacrolimus levels sevenfold and cyclosporine levels threefold, so the regimen requires dose adjustment and close monitoring. In the clinical trial, tacrolimus was given only once a week (0.5 mg) and the cyclosporine dose was reduced to one-fifth of the pretreatment dose. Treatment was well tolerated, and only one person, as noted above, discontinued treatment because of side effects. The common side effects were headache, fatigue, cough, and insomnia, and there were only two serious adverse events.

More recently, ledipasvir-sofosbuvir (Harvoni) in combination with ribavirin was tested in 223 people (of whom 112 had developed cirrho-

sis) with recurrent hepatitis C infection. Most (approximately 90 percent) of these individuals had undergone previous treatment for hepatitis C. Half of the participants were treated for 12 weeks and the other half for 24 weeks. In this study, duration of treatment did not make any difference, and 96 percent of individuals with mild fibrosis (108 of 111) or with Child A cirrhosis (49 of 51) were cured. The cure rate was 85 percent for those with Child B cirrhosis (38 of 44), but only 60 percent for Child C (5 of 8). Although this drug combination has not been approved by the FDA for treating recurrent hepatitis C, it is perhaps the best treatment option currently available for genotype 1 infection in liver transplant recipients. Unlike the AbbVie regimen, Harvoni in combination with ribavirin results in very little interaction with the immunosuppressive regimen.

Retransplantation

Because retransplantation for people who have hepatitis C has had inferior outcomes compared with retransplantation for other indications, many transplant centers do not perform retransplantation for people who have recurrent hepatitis C cirrhosis. This attitude is likely to change with the availability of better medications to treat recurrent hepatitis C, and people who have recurrent hepatitis C cirrhosis and need retransplantation are likely to have outcomes similar to those of people who receive transplants for other indications. More importantly, the availability of and better cure rates with interferon-free regimens will reduce the recurrence rates and disease progression for most people, leading to a decreased demand for retransplantation in the future.

Part III

Complementary and Alternative Medicine

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Complementary and Alternative Medicine in the Treatment of Liver Disease and Hepatitis C

The National Center for Complementary and Alternative Medicine defines complementary and alternative medicine (CAM) as "a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine." Estimates indicate that 20 percent of the U.S. population takes herbal preparations. Natural remedies represent an approximately $200 billion per year global market.

Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, herbs are classified as dietary supplements. Under this law, supplements are broadly defined as "anything that supplements the diet" and include vitamins, minerals, herbs, amino acids, enzymes, and herbal extracts. The FDA has little regulatory control over dietary supplements, and therefore these products remain unregulated. Unlike drugs approved by the FDA, supplements can be sold without manufacturers' or regulators' demonstration of clinical benefits. Though marketers cannot make explicit health claims for a supplement ("cures cancer"), they can promote its known effect on the "structure and function" of the body ("protects against cell damage"), and they can give the product any name they like ("Tumor Be Gone").

The use of herbal plants and alternative techniques such as acupuncture was originally confined to Asia and Africa but has now become universal. The use of herbal medicines can be traced as far back as 2100 BC in ancient China (the Xia dynasty) and India (the Vedic period). The

Table 19.1. Complementary and Alternative Medicines Used in the Treatment of Liver Disease

Supplements or Medications		
Defined Formulations	*Poorly Defined Formulations*	*Techniques*
Silymarin	TJ-19	Acupuncture
Phyllanthus amarus	Compound 861	Prayer
St. John's wort	Liv 52	Spirituality
Glycyrrhizin	CH-100	Massage therapy
	Homeopathy	Hypnotherapy
	Ayurvedic medicine	Energy therapy
	Traditional Chinese medicine	

current increase in the use of alternative medicine by people who have liver disease could be attributed partly to the failure of conventional treatments to cure common diseases such as hepatitis B and C and, more recently, non-alcoholic fatty liver disease. We may see a decline in the use of herbal preparations as the treatment of hepatitis B and C continues to improve. Another reason for the popularity of herbal preparations is the perception that they are "natural" and therefore a safer form of therapy. The holistic and spiritual appeal of these substances also attracts people who have chronic diseases to these forms of treatment.

Many herbal preparations are used by people who have liver disease, including preparations that fall within "mainstream" homeopathic, traditional Chinese, and Ayurvedic medicine. A discussion of all such preparations is beyond the scope of this book, but this chapter focuses on some commonly used herbal medicines and supplements available in the United States. The loose classification of CAM used in treating liver disease that is shown in table 19.1 is not complete by any standards.

Herbal Products

In U.S. surveys, more than one in three people (30 to 60 percent) who had liver disease said they were using naturopathic remedies; the most common preparation was milk thistle, followed by green tea, St. John's

wort, and dandelion root. Many people were taking multiple preparations. A significant majority of people did not tell their physician that they were using herbal preparations. Moreover, follow-up surveys show that the use of herbal preparations and supplements is increasing in the United States and other countries.

A scientific review of herbal preparations is challenging because many of these preparations are not standardized and often contain concoctions of various extracts. Because these products are unregulated, preparations marketed under the same or similar names might have completely different compositions. Most of the herbal products available on the market have not been tested in clinical trials. When tested, the measures used (the end points) are often subjective (feeling good, having more energy, and so on) rather than reproducible data (such as clearance of the virus, improvement in liver biopsy findings, decrease in the size of a tumor). In addition, the toxicity of herbal remedies—their harmful effects—is poorly reported on or documented. Some herbal preparations may also contain (deliberately mixed in) subtherapeutic doses of conventional (allopathic) medications, making matters worse as far as clinical tests are concerned.

Some commonly used preparations are discussed in the following sections.

Milk Thistle (Silymarin)

Milk thistle is a plant extract (from *Silybum marianum*); the name "milk thistle" is derived from the characteristics of the plant—its spiked leaves and white veins, which, according to legend, were believed to carry the milk of the Virgin Mary. Milk thistle is grown commercially throughout the United States. The active extract of milk thistle is silymarin, a mixture of plant compounds called flavonolignans, silydianin, silychristin, and silybin. Silybin (also called silibinin) makes up 60 to 70 percent of silymarin and is its most biologically active ingredient, with the remaining 20 to 30 percent being chemically undefined. Concentrations of silymarin are highest in the fruit of the plant, and are also high in the seeds and leaves, from which it is extracted with 95 percent ethyl alcohol to yield a bright yellow fluid. A standard silymarin extract contains

70 percent silymarin, but this can vary depending on the product and different batches of the same product.

As noted above, silybin is the major active ingredient of silymarin, and its pharmacological properties are well understood. In laboratory experiments, silybin shows antioxidant properties (that is, prevents the formation of chemicals called free radicals, which damage cells) and appears to protect liver cells and reduce inflammation and fibrosis, with little or no toxicity. In experiments with rats, silybin protects the liver against damage caused by carbon tetrachloride and acetaminophen (Tylenol). However, the clinical trials of silybin were done with only small numbers of people, were poorly designed, and used variable and subjective measures of its effects.

Many clinical trials have been conducted to assess the efficacy of silymarin for treating acute viral hepatitis. These trials were not conducted to usual scientific standards, and in many trials, the cause of the acute hepatitis was poorly defined and the follow-up period was short. The results showed inconsistent benefits, some showing favorable effects in the treatment groups, and others not showing any difference between the treated and untreated (control) groups. On the basis of the current evidence, the routine use of silymarin for the treatment of acute viral hepatitis (A or B) cannot be justified.

No good trials have been conducted on the use of silymarin for people who have chronic hepatitis B infection. There is some evidence that silymarin may inhibit hepatitis C viral replication, as shown in laboratory experiments and in studies of people receiving intravenous silybin. However, a well-designed clinical trial failed to show any benefit in improving liver enzymes in people with chronic hepatitis C infection for whom previous interferon and ribavirin treatment had failed. In this study, investigators tested different doses of silymarin (420 mg and 700 mg, and matching amounts of a placebo, administered three times a day for 24 weeks) and found no benefit in the treated group.

> In a well-conducted clinical trial, milk thistle failed to show any benefit for people infected with hepatitis C.

Silymarin also has been tested in people with alcohol-related liver disease. Some of these studies showed an improvement in liver enzymes in the treatment group compared with the control group, but there were no consistent improvements in serum bilirubin levels. In one study that explored the impact of silymarin on long-term survival of people who had alcoholic liver disease, a marginal survival advantage was found at one year and two years with silymarin treatment compared with placebo, despite no significant differences in biochemical measures. However, a subsequent study of 200 people with biopsy-proven cirrhosis failed to confirm a survival benefit. These studies highlight the difficulty in studying a heterogeneous group of patients and in using death as the end-point measure for a disease that is slowly progressive and has an unpredictable course.

> No side effects related to silymarin were observed in clinical trials, suggesting that silymarin is safe even at higher-than-customary doses.

Silymarin was tested in a small, poorly designed study of people who had primary biliary cirrhosis, and this study showed no improvements in liver enzymes or serum bilirubin. There is some experimental evidence showing that milk thistle may be beneficial for people who have nonalcoholic fatty liver disease.

Results of animal experiments show that silymarin is hepatoprotective (that is, protects the liver) against a variety of drugs and toxins. In uncontrolled clinical trials (meaning trials with no control, or placebo, group), there are reports of potential benefit (improvement in survival) for people with liver damage resulting from amanita intoxication (mushroom poisoning) who were treated with intravenous silymarin. However, most of the clinical trials assessing the efficacy of silymarin in treating liver damage caused by various toxins (such as chronic poisoning by organophosphates, toluene, and xylene) and by drugs (such as phenothiazines) involved only small numbers of people, and, not surprisingly, the results have been inconsistent.

Milk thistle is safe and has no known drug interactions. However, there is no firm evidence to suggest that it has any long-term benefits for people who have acute or chronic liver disease.

St. John's Wort

St. John's wort is a widely used herbal preparation with potentially serious drug-drug interactions with many medications, including medications used for the treatment of hepatitis C and as immunosuppressants (drugs used to suppress the immune system) after organ transplantation.

St. John's wort, an extract of the herb *Hypericum perforatum*, contains many pharmacologically active ingredients. The main ingredient is hyperforin, a substance that may have some beneficial properties for people who have depression (it inhibits the uptake by nerve cells of certain chemicals involved in depression). A large analysis of multiple studies (called a meta-analysis), covering 23 clinical trials using St. John's wort, showed that it was superior to a placebo in treating mild to moderate depression. There is no evidence that it is comparable or superior to commonly used antidepressants.

Many people who have hepatitis C use this herb, perhaps for its mood-elevating effect. There are many possible adverse effects, however, because of the potential herb-drug interaction with commonly used medications.

> St. John's wort induces the production of enzymes that eliminate some commonly used medications, including sofosbuvir and Viekira Pak, thereby reducing the blood levels of these medications and making them ineffective or less effective. If you are taking any medications and are considering taking St. John's wort, please ask your physician whether it is safe to do so.

For people who have undergone organ transplantation, there have been reports of serious transplant rejection with the concomitant use of St. John's wort, because it makes immunosuppressant medication less effective.

Glycyrrhizin

Glycyrrhizin, containing chemicals called sulfated saponins and lectins, is derived from the licorice root. It has been used for more than 20 years in Japan to treat chronic hepatitis. The standardized glycyrrhizin-containing aqueous extract, called Stronger Neo-Minophagen C (SNMC), has been tested in many people who have liver disease. This product is shown to protect liver cells and reduce inflammation. It may also have some properties against hepatitis B.

Clinical trials have shown improvement in liver enzymes and liver biopsy results in people with chronic hepatitis who took SNMC. For people who had hepatitis C, SNMC in combination with interferon produced improvement in liver enzymes without any effect on viral clearance. In a long-term study, SNMC reduced the development of liver cancer in people who had hepatitis C infection, but low potassium levels and hypertension were observed in 10 and 3 percent, respectively, of those treated with SNMC. These effects are thought to be related to its hormonal properties (resembling the effect of hormones called mineralocorticoids), and caution needs to be exercised when using this compound for people who have preexisting portal hypertension, as it may worsen peripheral edema and cause electrolyte abnormalities. Unless rigorous clinical studies confirm its benefit, it is better to avoid the use of SNMC for people who have portal hypertension.

Phyllanthus amarus

The Indian herb *Phyllanthus amarus*, known as "bahupatra" in India, contains compounds called hypophyllanthins and polyphenols and is said to have antiviral properties. Despite claims of the clearance of hepatitis B surface antigens in some clinical studies, there is no firm evidence that this substance is beneficial.

TJ-9 (Xiao chai hu tang or Sho-saiko-to)

The Chinese herbal medicine known as TJ-9 is widely used in Japan for the treatment of liver disorders. It is a dried mixture of seven herbs (from the roots of *Scutellaria*, *Glycyrrhiza*, *Bupleurum*, and ginseng; the

pinella tuber; the jujube fruit; and the ginger rhizome). The major alkaloids from *Scutellaria*, called baicalin and baicalein, are strong antioxidants and are known to inhibit cell proliferation and to induce apoptosis in liver cancer cells ("apoptosis" refers to biochemical changes that lead to "programmed cell death," which is a highly regulated process in normal cells). There are other potential properties, as shown in laboratory experiments, that may inhibit tumor growth and fibrosis.

Despite its wide use, there are few clinical trials with TJ-9. In a large study of 222 individuals who had chronic hepatitis and were treated with TJ-9 for 12 weeks, liver functions improved in the treatment group compared with the control group, and there were no adverse effects. The potential benefit of this compound in preventing liver cancer was also tested in a five-year study of 260 people who had cirrhosis. Rates of liver cancer development were similar in the treatment and control groups, but there was a trend favoring the treatment group for people who did not have hepatitis B. There was no difference in survival between treatment and control groups, suggesting that the benefits, if any, are marginal with this compound.

Compound 861

Compound 861, which comes from China, is an aqueous extract of many herbs. In laboratory experiments, it has been shown to reduce fibrosis. In uncontrolled clinical trials, it reduced markers of fibrosis, such as a protein called procollagen, found in serum. However, there are no well-conducted studies to show that this is an effective compound.

Liv 52

The Ayurvedic drug known as Liv 52, widely used in India, is an extract of several plants. As for many other herbs, there are animal experiments showing potential benefits. Some studies on people who had acute hepatitis reported improvement in liver enzymes, but these studies had no control group and thus it is difficult to draw any conclusions, especially since spontaneous improvement in liver enzyme levels is common in acute hepatitis. A two-year clinical trial comprising 188 people who had alcohol-related liver disease failed to show any survival benefit for people

with cirrhosis, and the death rate was higher in the treatment group for people who had more advanced (Child C) liver disease (81 percent versus 40 percent in the control group). Because of its potential toxicity, this drug should not be used by people who have liver disease until the manufacturers show a benefit in well-conducted and rigorous clinical studies.

Other Drugs and Herbal Products

CH-100 is a Chinese herb that has been used for treatment of hepatitis C, but no consistent beneficial effects have been identified so far. Many other compounds are used by people who have liver disease, including picroliv, thymosin, bing gan ling, kurorinone, iscador qu, and *Acanthopanax senticosus*. The active ingredients of these substances are mostly unknown, and there are no good trials showing any benefits. In general, these compounds should be avoided.

Homeopathy

Homeopathy is based on the belief that very tiny quantities of natural ingredients—such as sulfur, snake venom, duck liver, squid ink, mercury, arsenic, and a host of other natural compounds—may cure illnesses. Modern homeopathic mixtures are sometimes diluted a millionfold or more—often so many times that no active ingredients are left. Homeopathy was first introduced into the United States in 1825, and its use has recently increased, with homeopathic medicine sales increasing substantially in this country. Many people who have hepatitis C use homeopathic medications, but no clinical trials of these medications have been conducted.

Acupuncture

A survey conducted among people who had hepatitis C indicated that 1 in 10 had received acupuncture as an alternative attempt at therapy. Acupuncture has been studied in people who have hepatitis B and as an adjunctive treatment for pain following liver cancer surgery. There is no

evidence of benefit, and there is a potential risk, if sterile techniques are not employed, of contracting bloodborne infections.

Potential Liver Toxicity from Herbal and Dietary Supplements

There are many case reports or series of case reports on potential liver injury from herbal and dietary supplements. In the United States, findings suggest that 9 percent of drug-induced liver injury is due to dietary supplements. In the world literature, this varies from 2 to 70 percent, and the wide variation is mostly due to reporting bias. The list of liver-damaging supplements in table 19.2 is not complete, but can be used as a guide.

In addition to being damaging to the liver, many herbal preparations may interfere with the elimination of other commonly used medications (table 19.3). This interference can cause either low or high blood levels of other medications.

> Please let your doctor know that you are using any of these preparations if you are also taking other medications. Avoid them during hepatitis C treatment.

Table 19.2. Supplements with Potential for Causing Liver Damage

Indication for Use	*Supplements*
Joint problems	Flavocoxid (Limbrel), Schiff Move Free products, glucosamine (only weak evidence)
Pain control	Black cohosh, comfrey
Weight loss	Conjugated linoleic acid, ephedra (ma huang), germander, green tea, Herbalife products, Hydroxycut products, usnic acid
Gastrointestinal problem	*Aloe vera*, chaparral, greater celandine
Psychological problems	Kava-kava, skullcap, valerian
Other indications	Noni, pennyroyal, Liv 52

Table 19.3. Herbal Preparations and Other Substances That May Increase or Decrease Other Medication Levels

Danshen	Germander	Papaya
Devil's claw	Gingko biloba	Pyrrolizidines
Dong quai	Ginseng	Sho-saiko-to
Echinacea	Glycyrrhizin (licorice root)	St. John's wort
Feverfew	Grapefruit juice	Tamarind
Garlic	Kava-kava	

Coffee, Iron Supplements, and Vitamin D

Coffee

There is some evidence to suggest that consumption of two or more cups of coffee a day may prevent the development and progression of liver cancer. There may be other beneficial effects (improvement in liver enzymes, slower progression of fibrosis, higher cure rates with antiviral treatment) for other liver diseases, including fatty liver disease and hepatitis C.

Caffeine (in coffee and tea) is a naturally occurring methylxanthine, and in laboratory experiments it has been shown to prevent proliferation of cancer cells. In an 11-year European study, there was a 70 percent reduction of cancer risk in coffee drinkers and 40 percent reduction in tea drinkers. Meta-analysis of multiple studies has confirmed the benefit of coffee in cancer reduction; this benefit was seen in men and women, and regardless of the cause of liver disease—and even in those who consumed alcohol regularly. Low consumption of coffee was associated with a 30 percent reduction in liver cancer risk, and high consumption was associated with a 60 percent reduction. Based on these studies, it is reasonable to conclude that coffee drinking is beneficial for people with liver disease.

> There is evidence to suggest that coffee consumption is beneficial for people who have liver disease, and regular consumption of two or more cups of coffee will reduce liver cancer risk.

Iron Supplements or Iron-Rich Diet

Adequate iron intake is important to maintain normal levels of hemoglobin (the chemical that carries oxygen in red blood cells), and iron deficiency will lead to anemia. Iron absorption is controlled in the small intestine, but long-term ingestion of excess iron (in food or as supplements) may lead to "iron overload," which may lead to oxidative damage to cells (cause by free radicals). An excess body store of iron (measured as the chemical ferritin) is known to have harmful effects, including increased risk of liver cancer, in people with cirrhosis and may also result in rapid progression of fibrosis and lower cure rates with antiviral treatment.

> People who have liver disease should avoid iron supplements if they do not have iron deficiency. Please ask your doctor about the safety of using iron supplements if you do need to take them.

Vitamin D

Vitamin D has many functions, including maintaining bone density. Low bone density (osteopenia and osteoporosis) is common in people who have cirrhosis. Low vitamin D levels are common in the general population as well as in those with liver disease. Low vitamin D levels may lead to more rapid progression of fibrosis and may also reduce the cure rates with interferon-based antiviral treatment (interferon and ribavirin). It is very unlikely that low vitamin D levels will have a major impact with the new interferon-free treatments. Nevertheless, it is better to take vitamin D if blood levels show low levels, as vitamin D has many other beneficial effects. Excess vitamin D levels may be harmful, however, and people should avoid excess intake of vitamin D.

Safety of Acetaminophen (Tylenol)

Therapeutic doses of acetaminophen (less than 2,000 mg per day) are safe for the general population as well as for those who have chronic liver diseases, including cirrhosis. The only exception is for people who drink excessive amounts of alcohol. There is a general belief that people who

have liver disease should completely avoid acetaminophen. However, the body eliminates therapeutic doses of acetaminophen even in the presence of advanced cirrhosis, without any toxicity. Other pain medications, such as nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, etc.) may cause gastrointestinal bleeding and kidney toxicity, and such drugs should be avoided by people who have esophageal or gastric varices and those who have kidney dysfunction. It is my practice to advise individuals who have cirrhosis to use acetaminophen carefully (never to exceed 2,000 mg per day) for pain management and to avoid nonsteroidal anti-inflammatory drugs. Although narcotics could be used, they are likely to cause addiction and may precipitate hepatic encephalopathy (confusion) in people who have cirrhosis.

Herbal preparations are widely used by people who have liver disease, despite the absence of firm scientific evidence of their benefits. Some herbal preparations have been shown to improve liver enzymes without any positive impact on viral counts, liver biopsy results, or incidence of liver cancer. Some herbal preparations are associated with toxic effects or with herb-drug interactions (e.g., St. John's wort), while others, such as milk thistle (silymarin) and TJ-19, are relatively safe. There is a need for larger, well-designed trials to determine the efficacy or futility of herbal preparations in treating liver disease. Until then, physicians may continue to discourage the use of herbal preparations without a good safety record. Better education about commonly used CAM may be important to reduce any potentially harmful effects, while, at the same time, allowing the use of certain types of CAM as alternatives to or complementary to conventional medicine. There is increasing evidence that two or more cups of coffee a day may be beneficial for people who have chronic liver disease. Iron supplements should be used only in the presence of iron deficiency. People should consult with their physician before they decide to use any herbal preparations.

> Anyone who is planning to use an herbal preparation may also benefit from visiting the website (http://livertox.nih.gov) developed by the National Institutes of Health that examines the short-term and long-term safety of herbal preparations and dietary supplements.

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Patient Resources

Organizations

American Association for the Study of Liver Diseases
1001 North Fairfax Street, Suite 400
Alexandria, VA 22314
Tel: 703-299-9766
Fax: 703-299-9622
Email: aasld@aasld.org
www.aasld.org/patients/Pages/CommunityResources.aspx

American Liver Foundation
39 Broadway, Suite 2700
New York, NY 10006
Tel: 212-668-1000
Fax: 212-483-8179
Hepatitis C Helpline: 1-800-465-4837
http://hepc.liverfoundation.org

Centers for Disease Control and Prevention
Division of Viral Hepatitis
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
1600 Clifton Rd, Mailstop G-37
Atlanta, GA 30333
Tel: 1-800-CDC-INFO (1-800-232-4636)
TTY: 1-888-232-6348
www.cdc.gov/hepatitis/c

National Institute of Diabetes and Digestive and Kidney Diseases
LiverTox: Clinical and Research Information on Drug-Induced Liver Injury
http://livertox.nih.gov

Other Useful Organizations
HCV Advocate, www.hcvadvocate.org/hcsp/hcsp.asp
Hepatitis B Foundation, www.hepb.org
Hepatitis C Association, www.hepcassoc.org
Hepatitis Foundation International, http://hepfi.org

Clinical Trials

ClinicalTrials.gov, A Service of the U.S. National Institutes of Health, https://clinicaltrials.gov

Medication Assistance Programs

AbbVie, www.abbviehcv.com
Genentech Patient Assistance for Pegasys and Copegus, 888-941-3331
Gilead Patient Assistance for Sovaldi, 855-769-7284; www.mysupportpath.com
Johnson & Johnson Patient Assistance Foundation, 800-652-6227; www.jjpaf.org
Medicare, www.medicare.gov
Merck Patient Assistance for Victrelis, PegIntron, and Rebetol, 866-939-4372
Olysio Support (Medicare Excluded), 855-5-OLYSIO; www.olysio.com
Patient Access Network (PAN) Foundation, for underinsured patients, 866-316-PANF; www.panfoundation.org
RxAssist, Patient Assistance Program Center, www.rxassist.org

Finding a Specialist

American Association for Study of Liver Diseases, www.aasld.org
American Gastroenterological Association, www.gastro.org
American Liver Foundation, www.liverfoundation.org
Infectious Disease Society of America, www.idsociety.org

Liver Transplantation

United Network for Organ Sharing (UNOS)
1100 Boulders Parkway, Suite 500
P.O. Box 13770
Richmond, VA 23225-8770
Tel: 1-804-330-8602
www.unos.org

MELD Calculation

Organ Procurement and Transplantation Network, Allocation Calculator, http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp

Drug Interactions

University of Liverpool
www.hep-druginteractions.org

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